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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A61K 31/335, 31/38, 31/40, 31/41, 31/415, 31/44, 31/445, 31/55, C07D 207/09, 207/44, 211/26, 211/28, 213/04, 223/04, 213/12, 235/04, 235/06, 235/12, 235/14, 249/16, 249/18, 317/08, 317/28, 333/02, 333/04, 333/26, 333/36, 403/06, 405/06, 409/06, 487/02, 487/04</p>	<p>A1</p>	<p>(11) International Publication Number: WO 00/04900 (43) International Publication Date: 3 February 2000 (03.02.00)</p>
<p>(21) International Application Number: PCT/US99/12398 (22) International Filing Date: 20 July 1999 (20.07.99) (30) Priority Data: 60/093,387 20 July 1998 (20.07.98) US (71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US). (72) Inventors: YU, Kuo-Long; 139 Treadwell Street, Hamden, CT 06517 (US). CIVIELLO, Rita, Lee; 90 Cow Hill Road, Killingworth, CT 06419 (US). KRYSTAL, Mark, R.; 12 Salem Road, Westport, CT 06880 (US). KADOW, Kathleen, F.; 9 Quarry Run, Wallingford, CT 06492 (US). MEANWELL, Nicholas, A.; 15 Valli Drive, East Hampton, CT 06424 (US). (74) Agent: DUBOFF, Samuel, J.; Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.</p>	
<p>(54) Title: SUBSTITUTED BENZIMIDAZOLE ANTIVIRAL AGENTS (57) Abstract The present invention concerns antiviral compounds, their compositions, and use in the treatment of viral infections. More particularly, the invention provides benzimidazole derivatives for the treatment of respiratory syncytial virus infection.</p>		

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5 **SUBSTITUTED BENZIMIDAZOLE ANTIVIRAL AGENTS****BACKGROUND OF THE INVENTION**1. **Field of the Invention**

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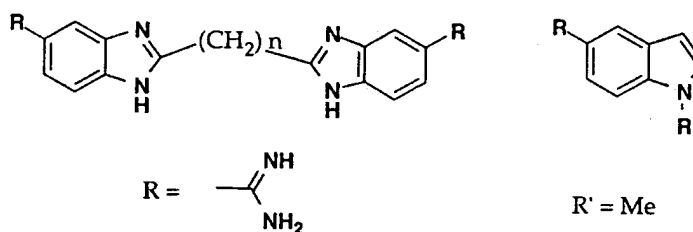
The present invention concerns antiviral compounds, their methods of preparation and their compositions, and use in the treatment of viral infections. More particularly, the invention provides benzimidazole derivatives for the treatment of respiratory syncytial virus
15 infection.

2. **Background Art**

Respiratory syncytial virus (RSV) is the leading cause of serious
20 lower respiratory tract infection in infants, children, elderly and immunocompromised persons. Severe infection of the virus may result in bronchiolitis or pneumonia which may require hospitalization or result in death. (*JAMA*, 1997, 277, 12). Currently only Ribavirin is approved for the treatment of this viral infection. Ribavirin is a
25 nucleoside analogue which is administered intranasally as an aerosol. The agent is quite toxic, and its efficacy has remained controversial. RespiGam, approved for prophylaxis in high risk pediatric patients, is an intravenous immunoglobulin which effectively neutralizes the virus. Recently, Synagis, a monoclonal antibody administered through
30 intramuscular injection has also been approved for use in high risk pediatric patients. However, both drugs are very expensive. Accordingly, inexpensive, safe and effective antiviral agents against respiratory syncytial virus will be beneficial for patients.

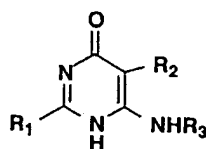
35 Many agents are known to inhibit respiratory syncytial virus (De Clercq, *Int. J. Antiviral Agents*, 1996, 7, 193). Y. Tao et al. (EP 0 058 146 A1, 1998) disclosed that Ceterizine, a known antihistamine, exhibited anti-

- 5 RSV activity. Tidwell et al., *J. Med. Chem.* 1983, 26, 294 (US Patent 4,324,794, 1982), and Dubovi et al., *Antimicrobial Agents and Chemotherapy*, 1981, 19, 649, reported a series of amidino compounds with the formula shown below as inhibitors of RSV.



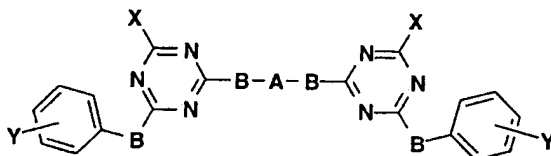
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Hsu et al., US Patent 5,256,668 (1993) also disclosed a series of 6-aminopyrimidones that possess anti-viral activity against RSV.



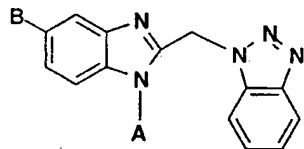
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- In addition, Y. Gluzman, et al., (AU Patent, Au-A-14,704, 1997) and P. R. Wyde et al. (*Antiviral Res.* 1998, 38, 31) disclosed a series of triazine containing compounds that were useful for the treatment and/or
- 20 prevention of RSV infection.

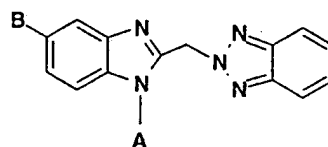


- This invention relates to the antiviral activity against RSV found
- 25 in a series of 1-substituted 2-(benzotriazolylmethyl)-benzimidazoles. Some of the compounds in our invention were first disclosed by F. Pagani and F. Sparatore in *Boll Chim Farm.* 1965, 104, 427 and by G. Paglietti, et al. in *Il Farmaco, Ed. Sci.* 1975, 30, 505, and found to possess analgesic and

- 5 anti-arrhythmic activity. The structural formula for these compounds are depicted in Formula Ia and Ib.

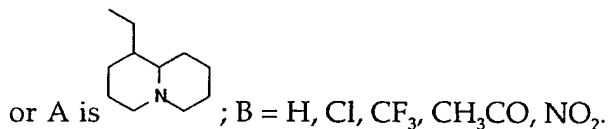


Formula Ia

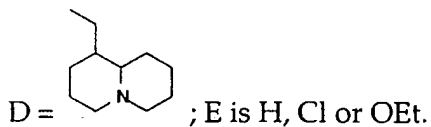


Formula Ib

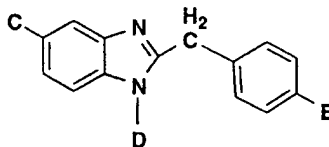
- 10 In Formula Ia and Ib, A is $-(CH_2)_n-N(R)_2$, $n = 2$ or 3 , $R = \text{Me}$ or Et ,



- Another series of closely related compounds that Sparatore had disclosed were in *Il Farmaco Ed. Sci.* 1967, 23, 344 (US patent 3,394, 141, 15 1968). Some of the compounds were reported to have analgesic, anti-inflammatory or anti-pyretic activities. The structure of these compounds is depicted in formula Ic. In Formula Ic, $C = \text{H}, \text{CF}_3$, or NO_2 . D is $-(CH_2)_n-$ NR₂, $n = 2$ or 3 , $R = \text{Me}$ or Et , or

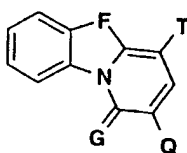


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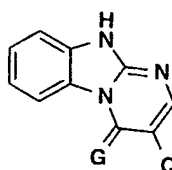


Formula Ic

5 Another series of compounds structurally related to this invention are pyrido[1,2-a]benzoxazoles and pyrimidio[1,2a]benzimidazoles disclosed by S. Shigeta et al in *Antiviral Chem. & Chemother.* 1992, 3, 171. These compounds have demonstrated inhibition of orthomyxovirus and paramyxovirus replication in HeLa cells. The structures of these
 10 compounds are shown in formulas Id and Ie, in which F = NH, S, or O; Q = -NHCOPh, -COOH, COOEt, or CN; T = COMe, CN, or COOEt; G = O or NH.

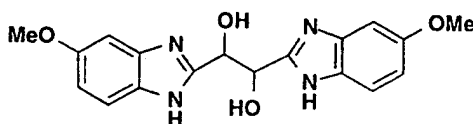


Formula Id

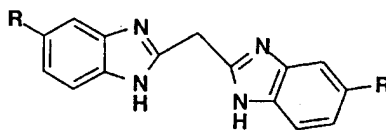


Formula Ie

15 A bis-benzimidazole with an ethylenediol linker shown below has also been reported as a potent inhibitor of rhinoviruses (Roderick, et al. *J. Med. Chem.* 1972, 15, 655.



20 Other structurally related compounds are bis-benzimidazoles which possess antifungal activity (B. Cakir, et al. *Eczacilik Fak. Derg.* 1988, 5, 71.



R = H, NO₂

25 Compounds of the present invention are benzimidazole derivatives and pharmaceutically acceptable salts thereof.

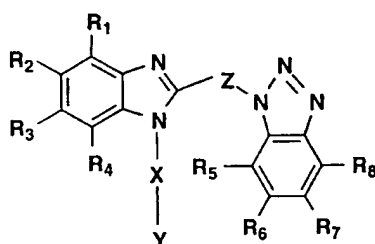
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Other prior art related to the chemical structure of the present invention:

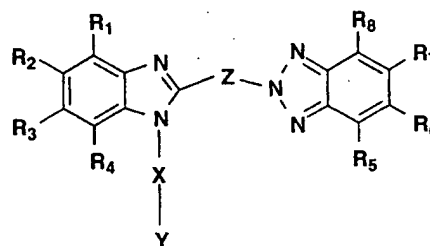
- (1) F. Sparatore, et al, "Derivati Benzotriazolici Attivi
10 Sull'accrescimento Delle Piante," *Il Farmaco Ed. Sci.* 1978, 33, 901.
- (2) Katritzky, A. R. et al, "Synthesis and Transformations Of
Substituted Benzazolyl- and Tetrazolyl(benzotriazol-1-yl)methanes," *J.*
Heterocyclic Chem. 1996, 33, 1107.
- 15 (3) Terri A. Fairley, et al. " Structure, DNA Minor Groove Binding,
And Base Pair Specificity of Alkyl and Aryl-Linked
Bis(amidinobenzimidazoles) and Bis(amidinoindoles), *J. Med. Chem.*
1993, 36, 1746.
- 20 (4) R. K. Upadhyay et al, " New Synthesis and Biological Evaluation,"
Indian J. Heterocyclic Chem. 1994, 4, 121.
- (5) A. R. Katritzky, et al, " A New Route to N-substituted Heterocycles,"
25 *Tetrahedron*, 1993, 49, 2829.

SUMMARY OF THE INVENTION

30 The present invention relates to compounds having the Formula II
and Formula III



Formula II



Formula III

wherein:

- $R_1, R_2, R_3, R_4, R_5, R_6, R_7$ and R_8 are independently H, alkyl, alkyl substituted with 1 to 6 halogen atoms, NO_2 , CN, halogen, COR' , COOR' , and CONHR' , R' is H or alkyl, and said alkyl contains 1 to 6 carbon atoms;

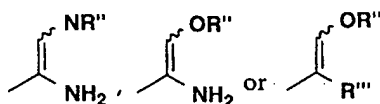
X is straight, branched or cyclic alkyl, alkenyl, and alkynyl groups, wherein said groups have 2 to 12 carbon atoms;

Y is selected from:

- (a) R_9 , $-\text{NR}_9\text{R}_{10}$, $-\text{NR}_9\text{R}_{10}\text{R}_{11}$, $-\text{NHCOR}_9$, $=\text{N-O-R}_9$, $-\text{CONHR}_9$, $-\text{COOR}_9$, $-\text{CO-R}_9$, $-\text{OR}_9$,

wherein R_9 , R_{10} and R_{11} are independently H, straight, branched or cyclic alkyl containing 1 to 7 carbon atoms; or R_9 taken together with R_{10} forms a cyclic alkyl group having 3 to 7 carbon atoms;

- (b) $-\text{N}_3$, $-\text{CN}$, halogen, $-\text{NO}_2$, $-\text{NR}''\text{SO}_2\text{R}'''$, $-\text{SR}''$, $-\text{SOR}''$, $-\text{SO}_2\text{R}''$, $-\text{SO}_2\text{NR}''$,



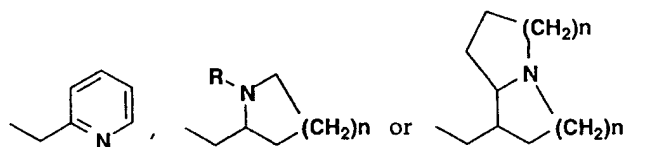
wherein said R'' and R''' are independently hydrogen, C_1 - C_6 alkyl, phenyl, or phenyl substituted with from 1 to 6 halogen atoms or C_1 - C_6 alkyl groups;

5

- (c) phenyl or heterocycle, selected from dioxolane, pyridine, pyrrole, thiophene, pyrrolidine or piperidine, and wherein said phenyl is optionally substituted with from 1 to 6 halogen atoms or C_1 - C_6 alkyl groups;

10

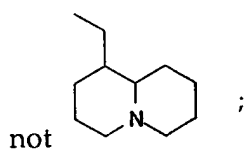
or X and Y taken together is selected from $-CH_2Ph$, $-CH_2COPh$, $-CH_2CHOHPh$,



- 15 wherein n is 1 or 2, R is C_1 - C_4 alkyl and Ph is phenyl;

Z is $-(CR_{12}R_{13})_n-$, wherein n is 1-4, and R_{12} and R_{13} are independently H, straight, branched or cyclic C_1 - C_6 alkyl;

- 20 provided when R_2 is H, Cl, CF_3 , CH_3CO or NO_2 ; R_1 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are not at the same time H; Z is not $(CH_2)_n$, where n is 1-3; X is not $(CH_2)_z$, where z is 2 or 3; Y is not $N(CH_3)_2$ or $N(C_2H_5)_2$ or X and Y taken together is



not

- 25 further provided when X and Y taken together is $-CH_2CH(CH_3)_2$, then Z is not CH_2 and R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are not each H at the same time.

A preferred embodiment are those compounds wherein:

30

- 5 $R_1, R_3, R_4, R_5, R_6, R_7$ and R_8 are each H; R_2 is H, C_1-C_3 alkyl, C_1-C_3 alkyl substituted with 1 to 6 halogen atoms, NO_2 , CN, halogen, COR' , $COOR'$, or $CONHR'$, wherein R' is H or C_1-C_3 alkyl;

X is $-(CH_2)_2-$ or $-(CH_2)_3$;

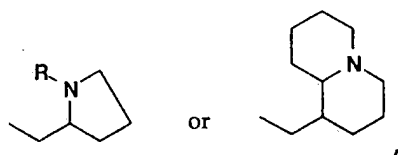
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Y is selected from

- 15 (a) H, straight, branched or cyclic C_1-C_7 alkyl;
 $-NR_9R_{10}$, $-^+NR_9R_{10}R_{11}$, $-NHCOR_9$, $-CO-R_9$, $-OR_9$, wherein
 R_9 and R_{10} are independently H, straight or branched C_1-C_3
 alkyl; or R_9 taken together with R_{10} forms a cyclic alkyl
 group having 5 to 7 carbon atoms;
- 20 (b) $-NHSO_2R''$, $-SR''$, $-SOR''$, $-SO_2R''$, wherein said R'' is C_1-C_3
 alkyl;

or X and Y taken together is selected from $-CH_2COPh$, $-CH_2CHOHPh$,

25



wherein R is C_1-C_3 alkyl; and

- 30 Z is CH_2 .

Another preferred embodiment are those compounds wherein:

5 $R_1, R_3, R_4, R_5, R_6, R_7$ and R_8 are each H; R_2 is H or halogen;

X is $-(CH_2)_2-$ or $-(CH_2)_3$;

Y is selected from

10

(a) H, straight, branched or cyclic C_1 - C_7 alkyl;
 $-NR_9R_{10}$, $-^*NR_9R_{10}R_{11}$, $-CO-R_9$, or $-OR_9$, wherein R_9 and
 R_{10} are independently H, straight, branched C_1 - C_3 alkyl; or
 R_9 taken together with R_{10} forms a cyclic alkyl group
15 having 5 to 7 carbon atoms;

(b) $-SR''$, $-SOR''$ or $-SO_2R''$, wherein said R'' is CH_3 ;

or X and Y taken together is $-CH_2COPh$ or $-CH_2CHOHPh$; and

20

Z is CH_2 .

In another embodiment of the invention there is provided a
method for treating mammals infected with RSV, and in need thereof,
25 which comprises administering to said mammal a therapeutically
effective amount of one or more of the aforementioned compounds
having the Formula II or Formula III, including pharmaceutically
acceptable salts thereof, but not subject to the proviso thereto.

30 Another embodiment includes a pharmaceutical composition
which comprises a therapeutically effective amount of one or more of the
aforementioned anti-RSV compounds having Formula II or Formula III,
including pharmaceutically acceptable salts thereof, and a
pharmaceutically acceptable carrier.

35

5 The term pharmaceutically acceptable salt includes solvates, hydrates, acid addition salts and quaternary salts. The acid addition salts are formed from a compound of Formula II or III compound and a pharmaceutically acceptable inorganic acid including but not limited to hydrochloric, hydrobromic, sulfuric, phosphoric, methanesulfonic, acetic,
10 citric, malonic, fumaric, maleic, sulfamic, or tartaric acids. Quaternary salts include chloride, bromide, iodide, sulfate, phosphate, methansulfonate, citrate, acetate, malonate, fumarate, sulfamate, and tartrate.

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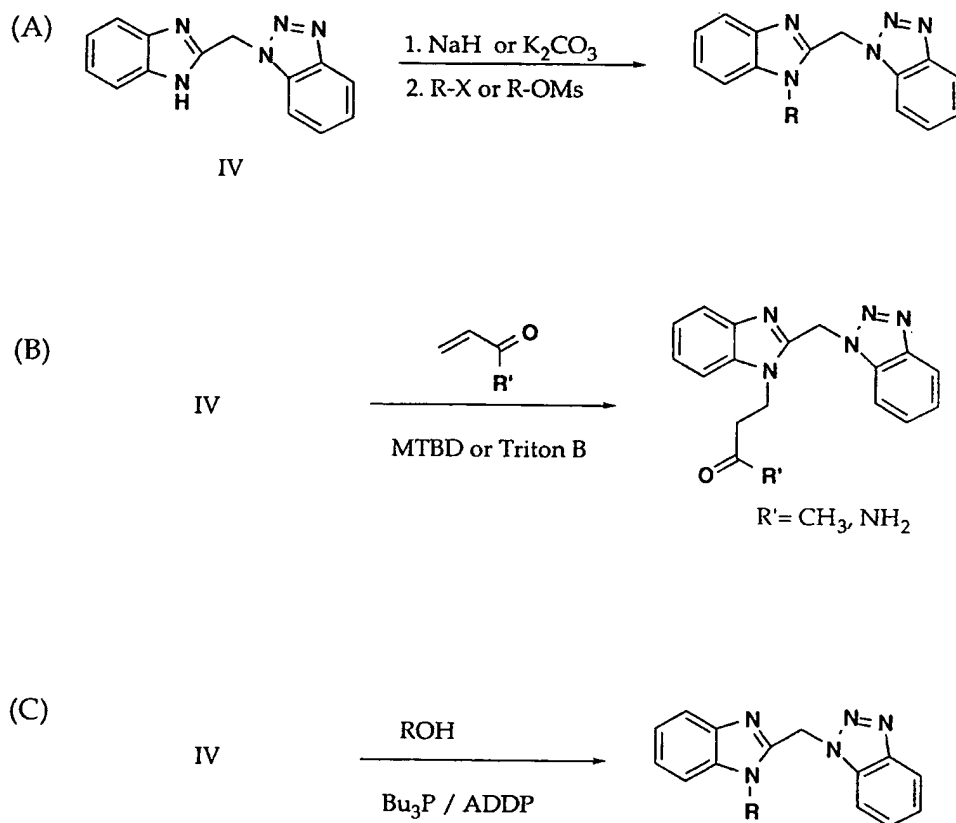
DETAILED DESCRIPTION OF THE INVENTION

Compounds of formula II and III may be prepared using the procedures described by F. Sparatore et al. in *Il Farmaco-Ed. Sci.* 1967, 23,
20 344, and by G. Paglietti, et al. in *Framco, Ed. Sci.* 1975, 30, 505.

Alternatively, compounds of formula II may be prepared from compound IV using the procedure described in Scheme I. The starting materials, however, are not particularly limited, and can be their
25 substituted derivatives so long as there is a free NH at the 1-position of the benzimidazole moiety. Compound IV and its derivatives can be prepared from the corresponding derivatives of benzotriazol-1-yl-acetic acid and phenylenediamine using the procedures described by A. Katritzky et al. (*J. Heterocyclic Chem.* 1996, 33, 1107) or by W. Siegart and
30 A. Day (*J. Am. Chem. Soc.* 1957, 79, 4391).

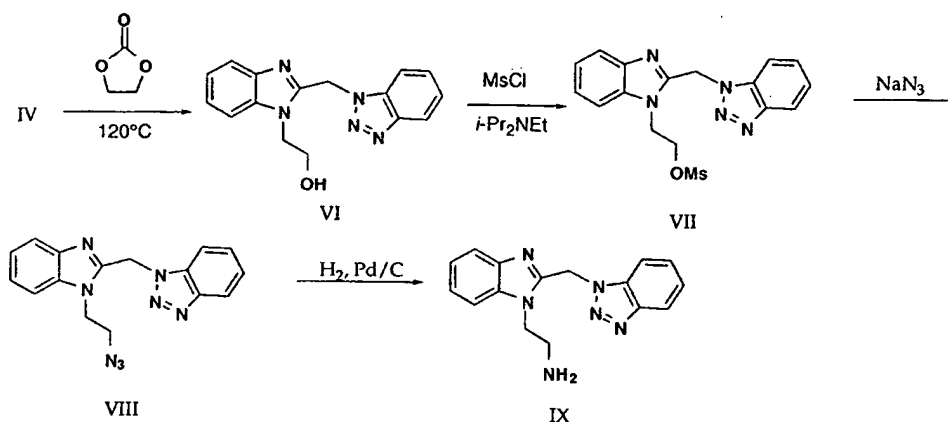
In Scheme IA, the starting material, compound of formula IV, is reacted with sodium hydride or potassium carbonate followed by the addition of the corresponding halides (RX) or alkylsulfonates (R-OMs) to
35 produce compounds of formula II. The compound in Formula II can also be prepared by reacting IV with acrylates, acrylamides or vinyl alkyl

- 5 ketones in the presence of 1,3,4,6,7,8-hexahydro-1-methyl-2H-pyrimido[1,2-a] pyrimidine (MTBD) or Triton-B, as shown in Scheme IB. The resulting amides or ketones can be reduced further by sodium borohydride, lithium aluminum hydride, or alane, to the corresponding amines or alcohols. In an alternative route (Scheme IC), the compound
- 10 in Formula II can be prepared by reacting compound IV with alcohols in the presence of 1,1'-(azodicarbonyl)-dipiperidine (ADDP) and tributylphosphine, as shown in Scheme Ic.

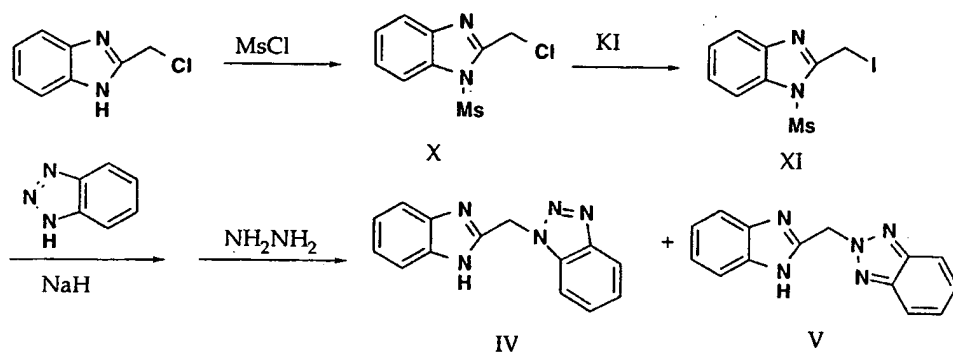
5 **Scheme I**

In a different route shown in Scheme II, compound of Formula IV can be heated with ethylene carbonate to afford the alcohol of formula VI.

- 10 Treatment of the alcohol with methanesulfonyl chloride and diisopropylethylamine produces the compound of Formula VII. Displacement of the mesylate with sodium azide gave the azido compound of Formula VIII. Reduction of the azide provides the amine of Formula IX.

5 **Scheme II**

The compounds of Formula III can be prepared using the same procedure described in Scheme I-II using compound V or its substituted derivatives as the starting material. Compound V can be prepared using the procedure described in F. Pagani and F. Sparatore in *Boll Chim Farm.* 1965, 104, 427. Alternatively, the compound can be prepared using the reaction sequence depicted in Scheme III. In Scheme III, 2-chloromethylbenzimidazole reacts with methanesulfonyl chloride (MsCl) and triethylamine to give compound of Formula X. The chloride can be refluxed with potassium iodide in acetone to produce the compound of Formula XI. N-alkylation of benzotriazole with compound XI, followed by removal of the mesylate protecting group with hydrazine in methanol affords a 10: 1 mixture of compounds of Formula IV and Formula V.

5 **Scheme III**

5 It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

10 It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician or veterinarian. In general however, a suitable dose will be in the range
15 of from about 0.01 to 750 mg/kg of body weight per day preferably in the range of 0.1 to 100 mg/kg/day, most preferably in the range of 0.5 to 25 mg/kg/day.

20 Treatment is preferably commenced before or at the time of infection and continued until virus is no longer present in the respiratory tract. However, the treatment can also be commenced when given post-infection, for example after the appearance of established symptoms.

25 Suitable treatment is given 1-4 times daily and continued for 3-7, e.g. 5 days post infection depending upon the particular compound used.

30 The desired dose may be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

 The compound is conveniently administered in unit dosage form, for example, containing 10 to 1500 mg, conveniently 20 to 1000 mg, most conveniently 50 to 700 mg of active ingredient per unit dosage form.

5 While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

10 The invention thus further provides a pharmaceutical formulation comprising a compound of the formula II or formula III, but not subject to the proviso thereto, or a pharmaceutically acceptable salt or derivative thereof together with a pharmaceutically acceptable carrier thereof.

15 The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

20 The pharmaceutical formulations may be in the form of conventional formulations for the intended mode of administration.

25 For intranasal administration according to the method of the invention the compounds of the invention may be administered by any of the methods and formulations employed in the art for intranasal administration.

 Thus in general the compounds may be administered in the form of a solution or a suspension or as a dry powder.

30 Solutions and suspensions will generally be aqueous, for example prepared from water alone (for example sterile or pyrogen-free water), or water and a physiologically acceptable co-solvent (for example ethanol, propylene glycol, and polyethylene glycols such as PEG 400).

35 Such solutions or suspensions may additionally contain other excipients, for example, preservatives (such as benzalkonium chloride),

5 solubilizing agents/surfactants such as polysorbates (e.g. Tween 80, Span 80, benzalkonium chloride), buffering agents, isotonicity-adjusting agents (for example sodium chloride), absorption enhancers and viscosity enhancers. Suspensions may additionally contain suspending agents (for example microcrystalline cellulose, carboxymethyl cellulose sodium).

10

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case a means of dose metering is desirably provided. In the case of a
15 dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomizing spray pump.

20

Intranasal administration may also be achieved by means of an aerosol formulation in which the compound is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), for example dichlorodifluoromethane, trichlorofluoromethane or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The
25 aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Experimental Section

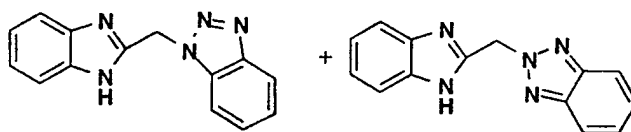
30

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker AC-300, Bruker DPX-300 or a Varian Gemini 300 spectrometer. All spectra were determined in CDCl_3 , CD_3OD , or DMSO-d_6 and chemical shifts are reported in δ units relative to tetramethylsilane
35 (TMS). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad peak; dd, doublet of doublets. Mass

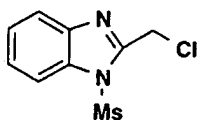
5 spectroscopy were performed on a Finnegan SSQ 7000 quadrupole mass spectrometer in both positive and negative electrospray ionization (ESI) modes, or on a Finnegan TSQ 700 triple quadrupole mass spectrometer in positive direct chemical ionization (DCI) mode with isobutane as reagent gas. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000
10 FTIR. Column chromatography was performed on silica gel from EM Science.

The synthesis of compounds in examples 1-4 and 51-53 was reported by F. Pagani et al. in *Boll Chim Farm.* 1965, 104, 427. Preparation
15 of compounds in examples 5-8 and 54-56 was described by G. Paglietti, et al. in *Il Farmaco, Ed. Sci.* 1975, 30, 505. Preparation of compounds in examples 9-50 and 57-61 is described as follows:

20 Synthesis of intermediate 1-(1H-Benzimidazol-2-ylmethyl)-1H-benzotriazole and 2-(1H-Benzimidazol-2-ylmethyl)-2H-benzotriazole



30 2-(Chloromethyl)-1-(methanesulfonyl)- benzimidazole



To a solution of 2-(chloromethyl)benzimidazole (80 g, 0.48 mol) and methanesulfonyl chloride (58.3 mL, 0.75 mol) in 0.5 L of methylene
chloride, triethylamine (136 mL, 0.97 mol) was added dropwise under
nitrogen. The resulting mixture was stirred at room temperature for 6
hours. The mixture was filtered and the filtrate was evaporated. The

5 residue was triturated in methanol and filtered to afford 74.9 g of the title compound as a brown solid.

IR (KBr, cm^{-1}): 3027, 2920, 1371, 1349, 1177, 1144, 1059.

^1H NMR (CDCl_3) δ 3.44 (s, 3 H), 5.11 (s, 2 H), 7.40-7.49 (m, 2 H), 7.76-7.82 (m,
10 1 H), 7.85-7.91 (m, 1 H).

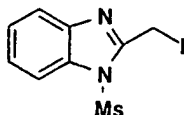
MS m/e 245 (MH^+)

Anal. Calcd for $\text{C}_9\text{H}_9\text{ClN}_2\text{O}_2\text{S}$: C, 44.18; H, 3.71; N, 11.45.

Found: C, 44.09; H, 3.57; N, 11.49.

15

2-(Iodomethyl)-1-(methanesulfonyl) benzimidazole



20 A solution of potassium iodide (206 g, 1.24 mol) and methanesulfonyl-2-chloromethyl benzimidazole (74.8 g, 0.414 mol) in 1 L of acetone was stirred at reflux under nitrogen for 4 hours. The solid was filtered and the filtrate was evaporated. The crude product was triturated in methanol and filtered to give 83 g of the title compound as a solid.

25

IR (KBr, cm^{-1}): 3022, 2916, 1366, 1173, 1055, 966, 763, 745.

^1H NMR (CDCl_3) δ 3.48 (s, 3 H), 4.97 (s, 2 H), 7.40-7.50 (m, 2 H), 7.75-7.85 (m,
2 H).

MS m/e 336 (MH^+)

30 Anal. Calcd for $\text{C}_9\text{H}_9\text{IN}_2\text{O}_2\text{S}$: C, 32.16; H, 2.70; N, 8.33.

Found: C, 32.05; H, 2.63; N, 8.22.

Benzotriazole (238 mg, 2 mmol) in 4 mL of anhydrous N,N-dimethylformamide was added sodium hydride (60% in mineral oil, 88

5 mg; 2.2 mmol). After stirring for 1 hour, 2-iodomethyl-1-methanesulfonyl benzimidazole (740 mg, 2.2 mmol) was added. The resulting solution was stirred for 6 hours, diluted with water, and extracted with diethyl ether. The combined extracts were dried over magnesium sulfate, and evaporated. To the residue was added 5 mL of
10 methanol and hydrazine (0.5 mL), and stirred at 65 °C overnight. The solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate, and evaporated. The residue was purified by flash chromatography (EtOAc: hexane = 1:1 to 2: 1) to give 24 mg (5 %) of 2-(1H-benzimidazol-2-ylmethyl)-2H-benzotriazole (IV), and 240 mg (48%) of 1-
15 (1H-benzimidazol-2-ylmethyl)-1H-benzotriazole (III) as solids.

1-(1H-Benzimidazol-2-ylmethyl)-1H-benzotriazole:

IR (KBr, cm^{-1}): 3140, 3057, 1452, 1441, 1272, 1229, 1099, 734.

20 ^1H NMR (CDCl_3) δ 6.23 (s, 2 H), 7.28-7.31 (m, 3 H), 7.46 (bt, $J = 7.3$ Hz, 1 H), 7.60-7.64 (m, 2 H), 7.67 (d, $J = 8.3$ Hz, 1 H), 7.85 (d, $J = 7.8$ Hz, 1 H)
MS m/e 250 (MH^+).

Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_5$: C, 67.46; H, 4.45; N, 28.09.

Found: C, 67.34; H, 4.57; N, 28.17.

25

2-(1H-Benzimidazol-2-ylmethyl)-2H-benzotriazole

IR (KBr, cm^{-1}): 1435, 1324, 1274, 855, 739.

^1H NMR (CDCl_3) δ 6.26 (s, 2 H), 7.25-7.31 (m, 2 H), 7.38-7.42 (m, 2 H), 7.59-7.61 (m, 2 H), 7.83-7.88 (m, 2 H).

30 MS m/e 250 (MH^+).

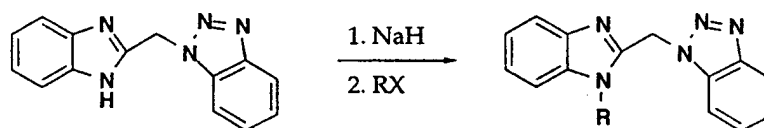
Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_5$: C, 67.46; H, 4.45; N, 28.09.

Found: C, 67.19; H, 4.54; N, 28.03.

35

5

General Procedure For Coupling of 1-(1H-Benzimidazol-2-ylmethyl)-1H-benzotriazole To Alkyl Halides:

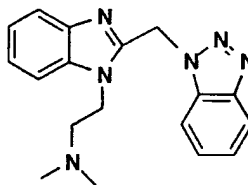


10

To 1-(1H-Benzimidazol-2-ylmethyl)-1H-benzotriazole (50 mg, 0.20 mmol) in 1.5 mL of solvent such as N,N-dimethylformamide, tetrahydrofuran, toluene or a mixture of solvents above, was added sodium hydride (60% suspension in mineral oil, 9 mg, 0.22 mmol) under nitrogen. After stirring for 30 minutes, the alkylhalide (0.22 mmol) was added. The reaction mixture was stirred overnight under nitrogen at a temperature ranging from 20 °C to 100 °C. The reaction mixture was diluted with saturated aqueous sodium bicarbonate solution and extracted with diethyl ether or ethyl acetate. The extracts were dried over magnesium sulfate, filtered, and evaporated. The crude product was purified by flash chromatography on silica gel using a mixture of solvents such as hexane, ethyl acetate, methylene chloride and methanol. The pure product obtained can also be converted to a salt such as the hydrogen chloride salt by treating the compound in methanol with excess 4 N HCl in dioxane and evaporating. The procedure was repeated two times and the residue was triturated with ether, and filtered to afford the salt.

30

5

Example 11-[1-(N,N-Dimethyl-aminoethyl)-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole Hydrochloride

10

The general coupling procedure was applied using 2-dimethylaminoethyl chloride hydrochloride and sodium hydride in tetrahydrofuran to give the title compound in 23% yield:

15 IR (KBr, cm^{-1}): 3446, 3383, 2697, 1613, 1466, 1457, 773, 753.

^1H NMR (CD_3OD) δ 3.14 (s, 6 H), 3.75-3.80 (m, 2 H), 5.24-5.29 (m, 2 H), 6.80 (bs, 2 H), 7.53-7.79 (m, 5 H), 8.07-8.14 (m, 3 H).

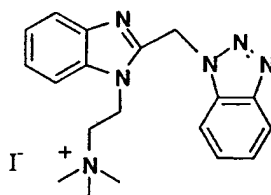
MS m/e 320 (MH^+)

Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_6 \cdot 2\text{HCl}$: C, 54.69; H, 6.12; N, 21.26; Cl, 17.94

20

Found: C, 54.49; H, 5.81; N, 21.20; Cl, 17.71.

5

Example 92-[2-(1H-Benzotriazol-1-ylmethyl)-1H-benzimidazol-1-yl]-ethyl
trimethylammonium iodide

10

The free base of 1-[1-(N,N-dimethyl-aminoethyl)-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole (100 mg, 0.312 mmol) was dissolved in anhydrous acetone. Methyl iodide (44 mg, 0.312 mmol) was added with stirring under N₂ at room temperature. After 3 hours, the white solid was filtered and dried under vacuum to give 19.5 mg (14%) of the title compound as a white solid.

IR (KBr, cm⁻¹): 3000, 1615, 1469, 1458, 740.

¹H NMR (CD₃OD) δ 3.41(s, 9 H), 3.62-3.68 (m, 2 H), 5.05-5.11 (m, 2 H), 6.43 (s, 2 H), 7.35-7.52 (m, 3 H), 7.60-7.72 (m, 3 H), 7.98 (bd, J = 7.5 Hz, 1 H), 8.05 (bd, J = 7.5 Hz, 1 H).

MS m/e 335 (M-I⁺).

Anal. Calcd for C₁₉H₂₃IN₆: C, 49.36; H, 5.01; N, 18.18.

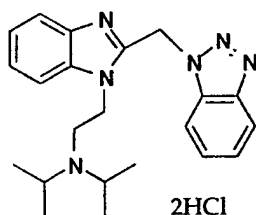
Found: C, 49.60; H, 4.86; N, 18.37.

25

5

Example 10**[2-(2-Benzotriazol-1-ylmethyl-benzimidazol-1-yl)-ethyl]-diisopropyl-amine Dihydrochloride**

10



The general coupling procedure was applied using 2-diisopropylaminoethyl chloride hydrochloride and sodium hydride in tetrahydrofuran to give the title compound in 51% yield:

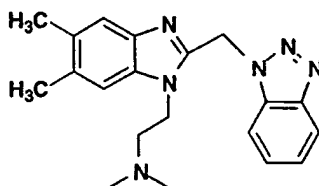
15

IR (KBr, cm^{-1}): 2914, 2649, 1614, 1465, 1356, 779, 747.

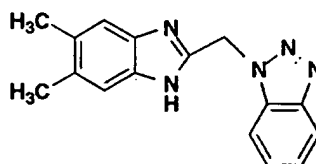
^1H NMR (CD_3OD) δ 1.51 (d, $J = 6.5$ Hz, 6 H), 1.56 (d, $J = 6.5$ Hz, 6 H), 3.72 (m, 1 H), 3.95-4.04 (m, 2 H), 5.37-5.43 (m, 2 H), 6.80 (s, 2 H), 7.52-7.81 (m, 5 H), 8.08-8.16 (m, 3 H).

20 MS m/e 377 (MH^+).**Example 11****[2-(2-Benzotriazol-1-ylmethyl-5,6-dimethyl-benzimidazol-1-yl)-ethyl]-dimethyl-amine**

25



5



4,5-Dimethyl-1,2-phenylenediamine (0.77g, 5.64 mmol) and 2-(1H-benzotriazol-1-yl)-acetic acid (1.0 g, 5.64 mmol) in polyphosphoric acid
10 (1.3g) at 175 °C was stirred for 2 hours. The reaction residue was added water and neutralized with sodium bicarbonate, and extracted with chloroform. The combined extracts were dried over magnesium sulfate and evaporated. The residue was triturated in hot ethyl acetate and filtered to give 564 mg of the product as a pale solid. The mother liquid
15 was evaporated, and the residue was triturated in ether to give an additional 672 mg of the product.

IR (KBr, cm^{-1}): 1448, 1164, 1108, 744.

^1H NMR ($\text{DMSO-}d_6$) δ 2.25 (s, 6 H), 6.15 (s, 2 H), 7.20 (bs, 1 H), 7.30 (bs, 1 H),
20 7.36 (bt, $J = 8.4$ Hz, 1 H), 7.45 (bt, $J = 8.4$ Hz, 1 H), 7.67 (d, $J = 8.4$ Hz, 1 H), 8.05 (d, $J = 8.4$ Hz, 1H).

MS m/e 278 (MH^+).

Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_5$: C, 69.30; H, 5.45; N, 25.25.

Found: C, 69.09; H, 5.41; N, 25.16.

25

The general coupling procedure was applied using 1-(5,6-dimethyl-1H-benzimidazol-2-ylmethyl)-1H-benzotriazole, 2-dimethylaminoethyl chloride hydrochloride and sodium hydride in N,N -dimethylformamide in 75% yield to give the title compound:

30

IR (neat, cm^{-1}): 3435, 2949, 2769, 1456, 1445, 1225, 745.

5 ^1H NMR (CDCl_3) δ 2.56 (s, 6 H), 2.33 (t, $J = 5.9$ Hz, 2 H), 2.35 (s, 6 H), 4.23 (s, 2 H), 7.09 (s, 1 H), 7.29-7.41 (m, 2 H), 7.56 (s, 1 H), 7.74 (d, $J = 8.2$ Hz, 1 H), 8.01 (d, $J = 8.2$ Hz, 1 H).

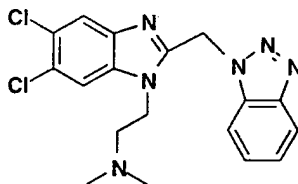
MS m/e 349 (MH^+)

Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_6 \cdot 0.125 \text{H}_2\text{O}$: C, 68.50; H, 6.97; N, 23.96.

10 Found: C, 68.28; H, 7.07; N, 24.12.

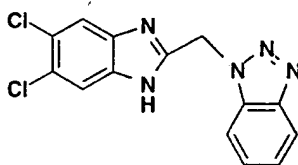
Example 12

15 [2-(2-Benzotriazol-1-ylmethyl)-5,6-dichloro-benzimidazol-1-yl]-ethyl-dimethyl-amine



20

1-(5,6-Dichloro-1H-benzimidazol-2-ylmethyl)-5,6-1H-benzotriazole



25 2-(1H-benzotriazol-1-yl)-acetic acid (1.0 g, 5.64 mmol) and 4,5-dichloro-1,2-phenylenediamine (1.0 g, 5.64 mmol) in 4 N HCl (40 mL) were stirred at reflux overnight. The solution was cooled to room temperature and neutralized with sodium bicarbonate. The mixture was extracted with tetrahydrofuran. The combined extracts were washed with
30 brine, dried over magnesium sulfate, and evaporated. The residue was

- 5 purified by flash chromatography (EtOAc:hexane=1:1 to straight EtOAc, gradient) to give a product which was triturated in ethyl acetate to give 425 mg of the product as a pink solid.

IR (KBr, cm^{-1}): 3128, 1443, 1309, 1096, 747.

- 10 ^1H NMR (DMSO-d_6) δ 6.28 (s, 2 H), 7.44 (t, $J = 6.9$ Hz, 1 H), 7.58 (t, $J = 6.9$ Hz, 1 H), 7.77 (s, 1 H), 7.85 (s, 1 H), 7.88 (d, $J = 8.3$ Hz, 1 H), 8.10 (d, $J = 8.3$ Hz, 1 H).

MS m/e 316 (M-H^+).

- 15 The general coupling procedure was applied using 1-(5,6-dichloro-1H-benzimidazol-2-ylmethyl)-5,6-1H-benzotriazole and 2-dimethylaminoethyl chloride hydrochloride in the presence of sodium hydride in N,N -dimethylformamide to give the title compound in 36% yield:

20

IR (KBr, cm^{-1}): 3436, 2787, 1464, 1446, 1080, 748.

^1H NMR (CDCl_3) δ 2.32 (s, 6 H), 2.45 (t, $J = 6.1$ Hz, 2 H), 4.31 (bs, 2 H), 6.26 (s, 2 H), 7.36-7.50 (m, 3 H), 7.77 (d, $J = 8.3$ Hz, 1 H), 7.91 (s, 1 H), 8.07 (d, $J = 8.3$ Hz, 1 H).

- 25 MS m/e 389 (MH^+).

Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{Cl}_2\text{N}_6$: C, 55.54; H, 4.66; N, 21.59.

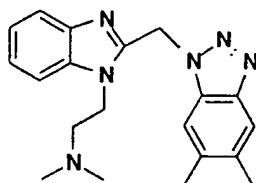
Found: C, 55.51; H, 4.84; N, 21.36.

5

Example 13

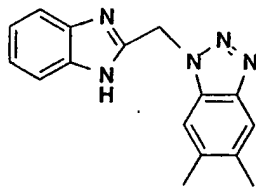
1-(1-(2-(5,6-Dimethylbenzotriazol-1-ylmethyl)-benzimidazol-1-yl)-ethyl)-
dimethyl-amine

10



1-(1H-Benzimidazol-2-ylmethyl)- 5,6-dimethyl-1H-benzotriazole

15



The same procedure described in the preparation of 1-(1H-benzimidazol-2-ylmethyl)-1H-benzotriazole was used, except that 5,6-dimethylbenzotriazole was used instead of benzotriazole. 1-(1H-benzimidazol-2-ylmethyl)- 5,6-dimethyl-1H-benzotriazole was isolated as an intermediate:

IR (KBr, cm^{-1}): 3433, 2944, 1624, 1587, 1421, 1221.

^1H NMR (CDCl_3) δ 2.32 (s, 3 H), 2.34 (s, 3 H), 6.10 (s, 2 H), 7.24-7.28 (m, 2 H), 7.37 (s, 1 H), 7.58 (bs, 2 H), 7.63 (s, 1 H).

MS m/e 278 (MH^+).

The general coupling procedure was applied using 1-(1H-benzimidazol-2-ylmethyl)- 5,6-dimethyl-1H-benzotriazole and 2-

- 5 dimethylaminoethyl chloride hydrochloride in the presence of sodium hydride in N,N-dimethylformamide to give the title compound in 11% yield:

IR (neat, cm^{-1}): 3404, 2949, 2466, 1625, 1463, 751.

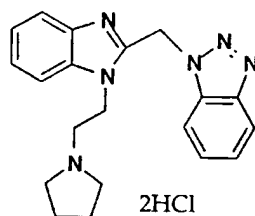
- 10 ^1H NMR (CD_3OD) δ 2.43 (s, 3 H), 2.49 (s, 3 H), 3.11 (s, 6 H), 3.58-3.64 (m, 2 H), 5.13-5.19 (m, 2 H), 6.59 (s, 2 H), 7.55-7.66 (m, 2 H), 7.76 (d, $J = 7.7$ Hz, 1 H), 7.82 (d, 1 H), 7.83 (d, $J = 6.6$ Hz, 1 H), 7.98 (d, $J = 8.0$ Hz, 1 H).
MS m/e 349 (MH^+).

15

Example 14

1-[1-(2-Pyrrolidin-1-yl-ethyl)-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole Dihydrochloride

20



- The general coupling procedure was applied using 1-(2-chloroethyl)-pyrrolidine hydrochloride and sodium hydride in tetrahydrofuran to give the title compound in 38% yield:

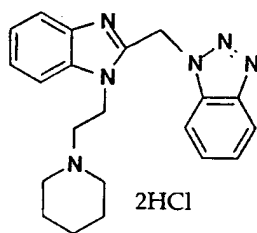
IR(KBr, cm^{-1}): 3412, 2929, 2465, 1800, 1615, 1520, 1457.

- ^1H NMR (CD_3OD) δ 2.13-2.26 (m, 4 H), 3.64-3.85 (m, 6 H), 5.05- 5.11 (m, 2 H), 6.59 (s, 2 H), 7.49-7.76 (m, 5 H), 7.89 (d, $J = 7.9$ Hz, 1 H), 8.02 (d, $J = 8.4$ Hz, 1 H), 8.09 (d, $J = 8.7$ Hz, 1 H).
MS m/e 347 (MH^+).

5

Example 151-(2-Piperidin-1-yl-ethyl)-1H-benzimidazol-2-ylmethyl)-1H-benzotriazole
Dihydrochloride

10



The general coupling procedure was applied using 1-(2-chloroethyl)-piperidine hydrochloride and sodium hydride in
15 tetrahydrofuran to give the title compound in 10% yield:

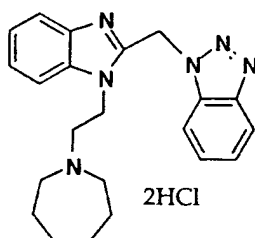
¹H NMR (CD₃OD) δ 1.95-2.15 (m, 6 H), 3.10-3.20 (m, 2 H), 3.50-3.80 (m, 4 H),
5.10-5.20 (m, 2 H), 6.62 (bs, 2 H), 7.50-7.76 (m, 5 H), 7.93 (d, J = 8.0 Hz, 1 H),
8.02 (d, J = 8.4 Hz, 1 H), 8.10 (d, J = 8.4 Hz, 1 H).

20 MS m/e 361 (MH⁺).

25

30

5

Example 161-(2-Azepin-1-yl-ethyl)-1H-benzimidazol-2-ylmethyl)-1H-benzotriazole
Dihydrochloride

10

The general coupling procedure was applied using 2-(hexamethyleneimino)ethyl chloride hydrochloride and sodium hydride in tetrahydrofuran to give the title compound in 27% yield:

15

IR(KBr, cm^{-1}): 3430, 2928, 2472, 1727, 1455, 1362.

^1H NMR (CD_3OD) δ 1.82 (bs, 4 H), 2.04 (bs, 4 H), 3.42-3.44 (m, 2 H), 3.56-3.74 (m, 4 H), 5.18-5.23 (m, 2 H), 6.67 (s, 2 H), 7.52-7.77 (m, 5 H), 8.00 (d, $J = 8.4$ Hz, 1 H), 8.04 (d, $J = 8.4$ Hz, 1 H), 8.11 (d, $J = 8.4$ Hz, 1 H).

20 MS m/e 375 (MH^+).

Anal. Calcd. for $\text{C}_{22}\text{H}_{26}\text{N}_6 \cdot 2\text{HCl} \cdot \text{H}_2\text{O}$: C, 56.16; H, 7.23; N, 13.10

Found: C, 56.28; H, 6.86; N, 13.27.

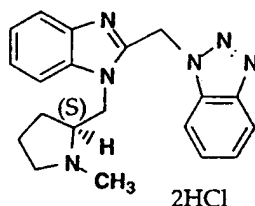
25

30

5

Example 17(S)-1-[1-Methyl-2-pyrrolidin-2-yl-methyl]-1H-benzimidazol-2-ylmethyl]-
1H-benzotriazole Dihydrochloride

10



The required (S)-2-(chloromethyl)-1-methylpyrrolidine hydrochloride was prepared according to the procedure reported by S. D. Kimball et al, *J. Med. Chem.* 1992, 35, 780-793. The general coupling
15 procedure was applied using sodium hydride as a base in N,N-dimethylformamide to give the title compound as a dihydrochloride salt (17% yield):

¹H NMR (CD₃OD) δ 2.00-2.30 (m, 4 H), 3.29 (s, 3 H), 3.56-3.90 (m, 2 H), 4.20-
20 4.30 (m, 1 H), 5.10 (dd, J = 9.3, 15.1 Hz, 1 H), 5.30 (dd, J = 5.7, 15.1 Hz, 1 H),
6.76 (bs, 2 H), 7.52-7.77 (m, 6 H), 8.01-8.13 (m, 2 H).
MS m/e 347 (MH⁺).

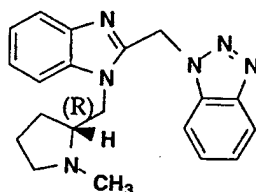
25

30

5

Example 18(R)-1-[1-Methyl-2-pyrrolidin-2-yl-methyl]-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole

10



The required starting material (R)-2-(chloromethyl)-1-methylpyrrolidine hydrochloride was prepared according to the procedure reported by S. D. Kimball et al, *J. Med. Chem.* **1992**, 35, 780-793 using (R)-N-methyl proline methyl ester (N.-H. Lin, et al. U.S. patent 5,424,444, 1995).
The general coupling procedure was applied using sodium hydride as a base in N,N-dimethylformamide to give the title compound in 23% yield:

IR (KBr, cm^{-1}): 2941, 2795, 1613, 1463, 1227, 755

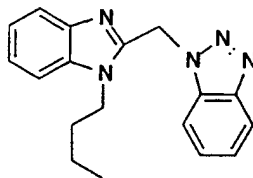
^1H NMR (CDCl_3) δ 1.50-1.59 (m, 1 H), 1.59-1.86 (m, 3 H), 1.96 (s, 3 H), 2.18-2.20 (m, 1 H), 2.65-2.74 (m, 1 H), 2.90-3.05 (m, 1 H), 4.06-4.23 (m, 2 H), 6.18 (d, $J = 15.3$ Hz, 1 H), 7.20-7.38 (m, 5 H), 7.72-7.76 (m, 2 H), 7.96 (d, $J = 8.3$ Hz, 1 H)

MS m/e 347 (MH^+).

Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_6$: C, 69.34; H, 6.40; N, 24.26
Found: C, 68.99; H, 6.49; N, 24.13.

30

5

Example 191-(1-Butyl-1H-benzimidazol-2-ylmethyl)-1H-benzotriazole

10

The general coupling procedure was applied using 1-bromobutane and sodium hydride in N, N-dimethylformamide to give the title compound in 61% yield:

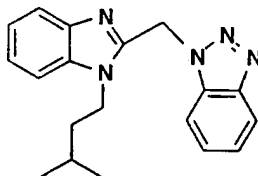
15 IR (KBr, cm^{-1}): 2957, 1471, 1440, 1328, 1230, 735.

^1H NMR (CDCl_3) δ 0.85 (t, $J = 7.1$ Hz, 3 H), 1.21-1.43 (m, 4 H), 4.20 (t, $J = 7.1$ Hz, 2 H), 6.18 (s, 2 H), 7.25-7.44 (m, 5 H), 7.75-7.83 (m, 2 H), 8.02 (d, $J = 8.3$ Hz, 1 H).

MS m/e 306 (MH^+).

20

5

Example 20**1-[1-(3-Methylbutyl)-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole**

10

The general coupling procedure was applied using 1-bromo-3-methylbutane and sodium hydride in N, N-dimethylformamide to give the title compound in 74% yield:

15 IR (KBr, cm^{-1}): 1474, 1453, 1091, 752, 736.

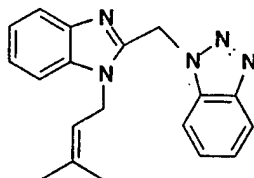
^1H NMR (CDCl_3) δ 0.91 (d, $J = 6.6$ Hz, 6 H), 1.17-1.25 (m, 2 H); 1.57-1.70 (m, 1 H), 4.19-4.24 (m, 2 H), 6.20 (s, 2 H), 7.25-7.45 (m, 5 H), 7.76-7.84 (m, 2 H), 8.03 (d, $J = 8.0$ Hz, 1H).

MS m/e 320 (MH^+).

20 Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{N}_5$: C, 71.45; H, 6.63; N, 21.93.
Found: C, 71.35; H, 6.72; N, 21.92.

Example 21

25

1-[1-(3-Methyl-2-butenyl)-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole

- 5 The general coupling procedure was applied using 1-bromo-3-methyl-2-butene and sodium hydride in tetrahydrofuran to give the title compound in 54% yield:

IR(KBr, cm^{-1}): 2930, 1614, 1464, 1418, 1086, 751.

- 10 ^1H NMR (CDCl_3) δ 1.58 (bs, 6H), 4.75-4.73 (m, 1 H), 4.83-4.85 (m, 2 H), 6.18 (s, 2 H), 7.25-7.44 (m, 5 H), 7.73 -7.82 (m, 2 H), 8.01 (d, $J = 8.2$ Hz, 1 H),
MS m/e 318 (MH^+).

Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{N}_5 \cdot 0.1\text{H}_2\text{O}$: C, 71.49; H, 6.06; N, 21.94

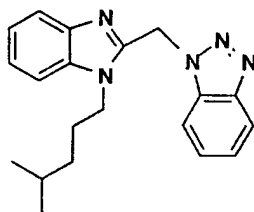
Found: C, 71.39; H, 6.20; N, 21.70

15

Example 22

1-[1-(4-Methylpentyl)-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole

20



- 25 The general coupling procedure was applied using 1-bromo-4-methylpentane and sodium hydride in tetrahydrofuran to give the title compound in 80% yield:

IR (KBr, cm^{-1}): 2956, 1475, 1457, 1087, 751, 736.

- ^1H NMR (CDCl_3) δ 0.98 (s, 9 H), 1.17-1.25 (m, 2 H), 4.20-4.25 (m, 2 H), 6.18 (s, 2 H), 7.25-7.44 (m, 5 H), 7.75-7.83 (m, 2 H), 8.03 (d, $J = 8.2$ Hz, 1 H),
30 MS m/e 334 (MH^+).

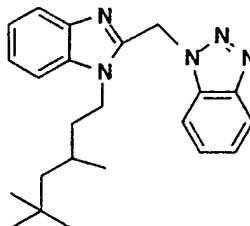
Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_5$: C, 72.04; H, 6.95; N, 21.00

Found: C, 71.73; H, 7.05; N, 21.06

5

Example 23**1-[1-(3,5,5-Trimethyl-hexyl)-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole**

10



The general coupling procedure was applied using 1-bromo-3,5,5-trimethylhexane and sodium hydride in tetrahydrofuran to give the title compound in 41% yield:

IR (KBr, cm⁻¹): 2953, 1614, 1506, 1472, 1459, 750, 737

¹H NMR (CDCl₃) δ 0.87 (s, 9 H), 0.99 (d, J = 6.6 Hz, 3 H), 1.04-1.23 (m, 3 H), 1.34-1.45 (m, 1 H), 1.53-1.57 (m, 1 H), 4.14-4.26 (m, 2 H), 6.19 (s, 2 H), 7.28-7.44 (m, 5 H), 7.76-7.83 (m, 2 H), 8.02 (bd, J = 8.4 Hz, 1 H).

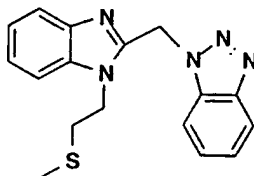
MS m/e 376 (MH⁺).

Anal. Calcd for C₂₃H₂₉N₅•0.5H₂O: C, 71.84; H, 7.86; N, 18.21

Found: C, 72.01; H, 7.82; N, 18.12

25

5

Example 241-[1-(2-Methylthio-ethyl)-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole

10

The general coupling procedure was applied using 2-chloroethylmethyl sulfide and sodium hydride in N, N-dimethylformamide to give the title compound in 44% yield:

15 IR (KBr, cm^{-1}): 1515, 1463, 1326, 1105, 738.

^1H NMR (CDCl_3) δ 2.05 (s, 3 H), 2.63 (t, $J = 6.9$ Hz, 2 H), 4.50 (t, $J = 6.9$ Hz, 2 H), 6.31 (s, 2 H), 7.29-7.37 (m, 4 H), 7.44 (t, $J = 7.5$ Hz, 1 H), 7.81-7.84 (m, 2 H), 8.03 (d, $J = 8.3$ Hz, 1 H).

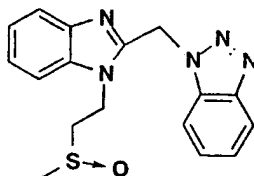
MS m/e 324 (MH^+)

20 Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{N}_5\text{S}$: C, 63.13; H, 5.30; N, 21.65
Found: C, 63.05; H, 5.08; N, 21.59

5

Example 251-[1-(2-Methylsulfinyl-ethyl)-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole

10



15 1-[1-(2-Methylthio-ethyl)-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole (100 mg, 0.31 mmol) was dissolved in acetic acid (5 mL). Sodium perborate tetrahydrate (52 mg, 0.34 mmol) was added. The reaction mixture was stirred at 50 °C under nitrogen overnight. The acetic acid was evaporated under reduced pressure. Column chromatography (EtOAc, then EtOAc: MeOH = 4:1) gave 84 mg (80%) of the title compound as a pale yellow solid.

20 IR (KBr, cm^{-1}): 3413, 1615, 1459, 1325, 1047, 743.

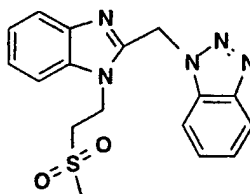
^1H NMR (CDCl_3) δ 2.53 (s, 3 H), 2.53-2.79 (m, 2 H), 4.68-7.47 (m, 1 H), 4.90-5.00 (m, 1 H), 6.20 (d, $J = 15.6$ Hz, 1 H), 6.37 (d, $J = 15.6$ Hz, 1 H), 7.28-7.39 (m, 3 H), 7.43-7.53 (m, 2 H), 7.78-7.82 (m, 1 H), 7.85 (d, $J = 8.4$ Hz, 1 H), 8.02 (d, $J = 8.4$ Hz, 1 H).

25 MS m/e 340 (MH^+).

Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{N}_5\text{OS} \cdot 2 \text{H}_2\text{O}$: C, 54.38; H, 5.64; N, 18.65.

Found: C, 54.15; H, 4.61; N, 18.07.

5

Example 26**1-[1-(2-Methylsulfonyl-ethyl)-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole**

10

1-[1-(2-Methylthio-ethyl)-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole (100 mg, 0.309 mmol) was dissolved in anhydrous N,N-dimethylformamide (5 mL). Magnesium monoperoxy phthalate hexahydrate (611 mg, 1.24 mmol) was added and the reaction mixture was stirred at room temperature overnight under N₂. The solvent was stripped under reduced pressure. The yellow oily residue was taken up in EtOAc (100 mL) and washed with water (2 X 50 mL) dried over magnesium sulfate, filtered and evaporated. Column chromatography on silica gel (EtOAc) gave 45 mg (41%) of the title compound as an oil.

20

IR (KBr): 2935, 1671, 1457, 1288, 1230, 1133, 754.

¹H NMR (CDCl₃) δ 2.95 (s, 3 H), 3.09 (t, J = 7.4 Hz, 2 H), 4.87 (t, J = 7.4 Hz, 2 H), 6.26 (s, 2 H), 7.30-7.40 (m, 4 H), 7.50 (t, J = 8.1 Hz, 1 H), 7.80-7.83 (m, 1 H), 7.84 (d, J = 7.5 Hz, 1 H), 8.04 (d, J = 1 H).

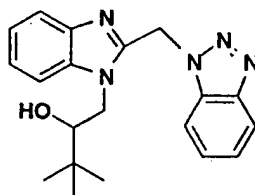
25

MS m/e 356 (MH⁺).

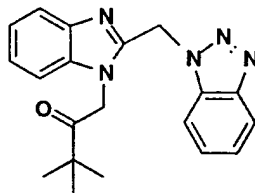
5

Example 271-(2-Benzotriazol-1-ylmethyl-1-H-benzimidazol-1-yl)-3,3-dimethylbutan-2-ol

10

1-(2-Benzotriazol-1-ylmethyl-1-H-benzimidazol-1-yl)-3,3-dimethylbutan-2-one

15



The general coupling procedure was applied using 1-bromopinacolone and sodium hydride in tetrahydrofuran to give the title compound in 61% yield:

20

IR (KBr, cm⁻¹): 2969, 1722, 1463, 1085, 749.

¹H NMR (CDCl₃) δ 1.30 (s, 9 H), 5.25 (s, 2 H), 6.09 (s, 2 H), 6.99-7.02 (m, 1 H), 7.49-7.25 (m, 4 H), 7.86-7.82 (m, 2 H), 7.99 (d, J = 7.5 Hz, 1 H),

MS m/e 348 (MH⁺).

25

Anal. Calcd. for C₂₀H₂₁N₅O: C, 69.14; H, 6.09; N, 20.16
C, 68.89; H, 6.20; N, 19.97.

To a solution of 1-(2-benzotriazol-1-ylmethyl-1-H-benzimidazol-1-yl)-3,3-dimethylbutan-2-one (75 mg, 0.216 mmol) in methanol (5 mL) was

5 added sodium borohydride (100 mg, 2.64 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for two hours and at room temperature for two hours. The solvent was removed, the residue was diluted with water, extracted with methylene chloride. The combined extracts were dried over magnesium sulfate. Solvent was evaporated to give 42 mg of the product.

10

IR(KBr, cm⁻¹): 3258, 2945, 2862, 1452, 1434, 1076, 743.

¹H NMR (CDCl₃) δ 1.12 (s, 9 H), 2.35 (d, J = 4.5 Hz, 1 H), 3.59-3.64 (m, 1 H), 4.41 (dd, J = 10.4, 14.8 Hz, 1 H), 4.25 (dd, J = 2.0, 14.8 Hz, 1 H), 5.96 (d, J = 15.4 Hz, 1 H), 6.58 (d, J = 15.4 Hz, 2 H), 7.21-7.46 (m, 5 H), 7.70-7.73 (m, 1 H), 7.82 (d, J = 8.3 Hz, 1 H), 8.00 (d, J = 8.3 Hz, 1 H).

15

MS m/e 350 (MH⁺).

Anal. Calcd. for C₂₀H₂₃N₅O•0.1H₂O: C, 68.39; H, 6.66; N, 19.94

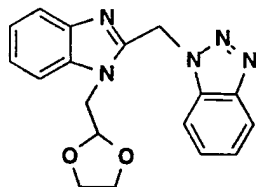
Found: C, 68.12; H, 6.72; N, 19.78.

20

Example 28

1-(2-[1,3]-Dioxolan-2-yl-methyl)-1H-benzimidazol-2-ylmethyl)-1H-benzotriazole

25



To a solution of 1-(1H-benzimidazol-2-ylmethyl)-1H-benzotriazole
30 (1.0 g, 4.0 mmol) in anhydrous dimethyl sulfoxide (10 mL) was added potassium tert-butoxide (1.94g, 4.0 mmol). The mixture was stirred at room temperature under nitrogen for 2 hours, followed by addition of a

- 5 solution of potassium iodide (40 mg) and 2-bromomethyl-1,3-dioxolane (1.94 g, 11.6 mmol) in anhydrous dimethyl sulfoxide (5 mL). The reaction was stirred overnight, and the resulting mixture was poured into saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated aqueous
- 10 sodium bicarbonate (2 x 20 mL), brine, dried over sodium sulfate, and evaporated. The residue was purified by flash chromatography (EtOAc-Hexane = 1:1) to give 152 mg (11%) of the title compound.

IR (KBr, cm⁻¹): 2887, 1464, 1439, 1416, 1082, 757, 740.

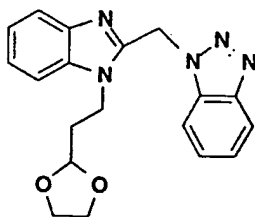
- 15 ¹H NMR (DMSO-d₆) δ 3.49-3.68 (m, 2 H), 3.71-3.78 (m, 2 H), 4.62 (d, J = 3.2 Hz, 2 H), 5.21 (t, J = 3.2 Hz, 1 H), 6.38 (s, 2 H), 7.10-7.25 (m, 2 H), 7.38-7.60 (m, 4 H), 7.75-7.83 (m, 1 H), 8.07 (d, J = 8.3 Hz, 1 H).

MS m/e 336 (MH⁺).

Anal. Calc for C₁₈H₁₇N₅O₂ : C, 64.47; H, 5.11; N, 20.88

- 20 Found: C, 64.17; H, 4.97; N, 21.27

5

Example 291-(2-[1,3]-Dioxolan-2-yl-ethyl)-1H-benzimidazol-2-ylmethyl)-1H-benzotriazole

10

The general coupling procedure was applied using 2-(2-bromoethyl)-dioxalane and potassium carbonate in N, N-dimethylformamide to give the title compound in 59% yield:

15

IR(KBr, cm⁻¹): 2883, 1614, 1512, 1409, 1131.

¹H NMR (CDCl₃) δ 1.92-1.98 (m, 2 H), 3.83-3.88(m, 2 H), 3.97-4.01 (m, 2 H), 4.46 (t, J = 7.1 Hz, 2 H), 4.83 (t, J = 4.4 Hz, 1 H), 6.25 (s, 2 H), 7.25-7.47 (m, 5 H), 7.80-7.85 (m, 2 H), 8.02 (d, J = 8.2 Hz, 1 H).

20 MS m/e 350 (MH⁺).

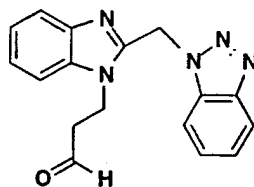
Anal. Calcd for C₁₉H₁₉N₅O₂•0.1H₂O: C, 64.98; H, 5.51; N, 19.94

Found: C, 64.75; H, 5.74; N, 19.76

25

30

5

Example 301-[(2-Benzotriazol-1-ylmethyl)-1-H-benzimidazol-1-yl]-propionaldehyde

10

1-(2-[1,3]Dioxolan-2-yl-ethyl)-1H-benzimidazol-2-ylmethyl)-1H-benzotriazole (100 mg, 0.286 mmol) in 3 mL of 1 N HCl was stirred at room temperature for 2 days. The reaction solution was neutralized with sodium bicarbonate and extracted with methylene chloride. The combined
15 extracts were dried over magnesium sulfate, and evaporated to give a white solid product.

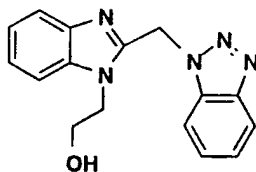
IR (KBr, cm^{-1}): 3416, 2923, 1711, 1610, 1464, 1095.

^1H NMR (CDCl_3) δ 2.72 (t, $J = 6.5$ Hz, 2 H), 4.59 (t, $J = 6.5$ Hz, 2 H), 6.29 (s, 2
20 H), 7.19-7.43 (m, 5 H), 7.72-7.82 (m, 2 H), 7.97 (d, $J = 8.1$ Hz, 1 H), 9.64 (s, 1 H),
MS m/e 306 (MH^+).

25

30

5

Example 312-(2-Benzoatriazol-1-ylmethyl-benzimidazol-1-yl)-ethanol

10

1-(1H-Benzimidazol-2-ylmethyl)-1H-benzotriazole (1g, 4 mmol) and ethylene carbonate (10g, 114 mmol) were stirred at 120°C for 7 hours. The reaction mixture was cooled and diluted with water. The aqueous layer was extracted with methylene chloride (3 x 150 mL). The combined organic layers were dried over magnesium sulfate, filtered, and evaporated. The residue was purified by flash chromatography (EtOAc/hexane=12:1) to give 375 mg (32%) of the title compound as a white solid.

20 IR (KBr, cm^{-1}): 3233, 2922, 1731, 1613, 1432, 1068, 746

^1H NMR (CDCl_3) δ 4.01-4.10 (m, 2 H), 4.70-4.73 (m, 2 H), 6.26 (s, 2 H), 7.25-7.45 (m, 5 H), 7.69 (d, $J = 7.6$ Hz, 1 H), 7.86 (d, $J = 8.4$ Hz, 1 H), 7.98 (d, $J = 8.4$ Hz, 1 H)

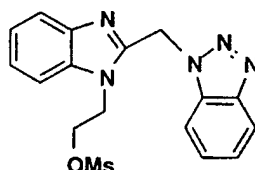
MS m/e 294 (MH^+).

25

5

Example 32Methanesulfonic acid, 2-(2-benzotriazol-1-ylmethyl-benzimidazol-1-yl)-ethyl ester

10



- 1-[1-(2-Hydroxyethyl)-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole (300 mg, 1.02 mmol) was suspended in anhydrous methylene chloride and cooled to 0°C with an ice bath.
- 15 Diisopropylethylamine (0.36 ml, 2.05 mmol) and methanesulfonyl chloride (0.16 mL, 2.05 mmol) were slowly added. The reaction was stirred at 0°C for 1 hour during which the solution became clear. The solvent was stripped under vacuum, and the residue was purified by flash chromatography (EtOAc) to give 221 mg (58%) of the title compound as a
- 20 white solid.

IR (KBr, cm^{-1}): 3015, 2935, 1617, 1514, 1460, 1339, 1162, 741

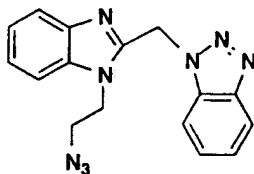
- ^1H NMR (CDCl_3) δ 2.75 (s, 3 H), 4.28 (t, $J = 5.5$ Hz, 2 H), 4.72 (t, $J = 5.5$ Hz, 2 H), 6.25 (s, 2 H) 7.31-7.40 (m, 4 H), 7.49 (bt, $J = 7.2$ Hz, 1 H), 7.81-7.84 (m, 1 H),
- 25 7.88 (d, $J = 8.3$ Hz, 1 H), 8.04 (d, $J = 8.4$ Hz, 1 H).

MS m/e 372 (MH^+)

Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{N}_5\text{O}_3\text{S}$: C, 54.98; H, 4.61; N, 18.86

Found: C, 54.90; H, 4.64; N, 18.58

5

Example 331-[1-(2-Azido-ethyl)-1-H-benzimidazol-2-ylmethyl]-1H-benzotriazole

10

Sodium azide (350 mg, 5.38 mmol) was added to a solution of methanesulfonic acid, 2-(2-benzotriazol-1-ylmethyl-benzimidazol-1-yl)-ethyl ester (200 mg, 0.54 mmol) in 5 mL of anhydrous N, N-dimethylformamide. The reaction temperature was raised to 105 °C and stirred for 4 hours. The mixture was cooled, diluted with water and extracted with diethyl ether (3x100 mL). The combined ether extracts were dried over magnesium sulfate, filtered, and evaporated under vacuum. This gave the title compound as a white solid (160 mg, 94% yield).

20 IR (KBr, cm^{-1}): 2955, 2122, 2097, 1616, 1514, 1464, 1329, 741.

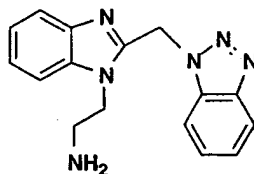
^1H NMR (CDCl_3) δ 3.50 (t, $J = 5.6$ Hz, 2 H), 4.40 (t, $J = 5.6$ Hz, 2 H), 6.21 (s, 2 H), 7.25-7.42 (m, 5 H), 7.75-7.80 (m, 2 H), 7.97 (d, $J = 8.3$, 1 H)

MS m/e 319 (MH^+).

Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_8$: C, 60.37; H, 4.43; N, 35.20

25 Found: C, 60.18; H, 4.48; N, 34.76

5

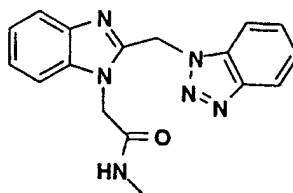
Example 342-(2-Benzotriazol-1-ylmethyl-benzimidazol-1-yl)-ethyl-amine

10

A mixture of 1-[1-(2-azido-ethyl)-1-H-benzimidazol-2-ylmethyl]-1H-benzotriazole (25 mg, 0.078 mmol) and 10% palladium on carbon in 1 mL of methanol was agitated under hydrogen at 55 psi for 5 hours. The reaction mixture was filtered through a pad of Celite and then through a Millipore membrane filter rinsing with methanol. The filtrate was stripped of solvent and dried under vacuum to give the amine (23 mg, quantitative yield) as a white solid.

¹H NMR (CD₃OD) δ 2.84 (t, d = 6.8 Hz, 3 H), 4.47 (t, J = 6.8 Hz, 3 H), 6.37 (s, 2 H), 7.25-7.35 (m, 2 H), 7.44 (t, d = 8.3 Hz, 1 H), 7.53-7.64 (m, 2 H), 8.00 (d, J = 7.7 Hz, 2 H), 8.03 (d, J = 8.2 Hz, 1 H).
MS m/e 293 (MH⁺).

25

Example 352-(2-Benzotriazol-1-ylmethyl-benzimidazol-1-yl)-N-methyl acetamide

5 1-(1H-Benzimidazol-2-ylmethyl)-1H-benzotriazole (500 mg, 2.00 mmol) was dissolved in anhydrous N,N-dimethylformamide (10 mL). Potassium carbonate (1.11 g, 8.00 mmol) and 2-chloro-N-methylacetamide (237 mg, 2.20 mmol) were added. The reaction mixture was allowed to stir overnight at reflux. The solvent was evaporated under vacuum, and the
10 white waxy residue taken up in methylene chloride (300 mL). The organic extract was washed with saturated aqueous sodium bicarbonate (2 x 100 mL), dried over magnesium sulfate, filtered and evaporated. The residue was purified by chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 15:1$) to give 304 mg (47%) of the title compound as a white solid.

15

IR (KBr, cm^{-1}): 3315, 1660, 1580, 1466, 1265, 745.

^1H NMR (CDCl_3) δ 2.55 (d, $J = 4.8$ Hz, 3 H), 4.93 (s, 2 H), 5.42 (bs, 1 H), 6.18 (s, 2 H), 7.27-7.39 (m, 4 H), 7.49 (dt, $J = 0.9, 8.2$ Hz, 1 H), 7.79-7.83 (m, 2 H), 8.04 (d, $J = 8.4$ Hz, 1 H).

20 MS m/e 320 (MH^+).

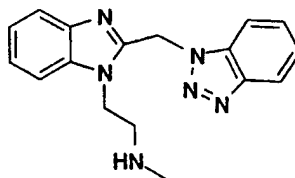
Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_6\text{O} \cdot 0.1 \text{H}_2\text{O}$: C, 63.38; H, 5.07; N, 26.09

Found: C, 63.09; H, 4.88; N, 26.19

25

Example 36

[2-(2-Benzotriazol-1-ylmethyl-benzimidazol-1-yl)-ethyl]-methyl-amine



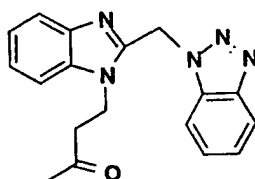
30

In an oven dried round bottom flask, lithium aluminum hydride (26 mg, 0.69 mmol) and aluminum chloride (97 mg, 0.73 mmol) were stirred in 10 mL of anhydrous tetrahydrofuran at 70-80°C for 1 hour. 2-(2-

5 Benzotriazol-1-ylmethyl-1-H-benzimidazol-1-yl)-N-methyl acetamide (50
mg, 0.156 mmol) was added. After 3 hours, more lithium aluminum
hydride (1 M in tetrahydrofuran, 0.312 mL, 0.312 mmol) was added. The
reaction mixture was allowed to stirred for 2 additional hours. The
solvent was evaporated, and the residue was purified by flash
10 chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}=15:1$) to give 14 mg (28%) of the title
compound as an oil.

^1H NMR (CDCl_3) δ 2.40 (s, 3 H), 2.73 (t, $J = 6.3$ Hz, 2 H), 4.41 (t, $J = 6.3$ Hz, 2
H), 6.29 (s, 2H), 7.25-7.46 (m, 5 H), 7.81 (bd, $J = 8.4$ Hz, 1 H), 8.01 (bd, $J = 8.3$
15 Hz, 1 H).

MS m/e 307 (MH^+).

Example 374-(2-Benzotriazol-1-ylmethyl)-benzimidazol-1-yl)-butan-2-one

10

1-(1H-Benzimidazol-2-ylmethyl)-1H-benzotriazole (0.20 g, 0.80 mmol) was suspended in acetonitrile (10 mL). Methyl vinyl ketone (67 mg, 0.962 mmol) was added followed by 1,3,4,6,7,8-hexahydro-1-methyl-2H-pyrimido[1,2-a] pyrimidine (MTBD, 6 mg, 0.040 mmol). The reaction mixture was heated at 80 °C overnight under nitrogen. The solvent was stripped under reduced pressure. The residue was taken up in ether and washed with water (2x 25 mL). The ether was dried over magnesium sulfate, filtered and evaporated. Column chromatography (CH₂Cl₂: MeOH= 20:1) gave 44 mg (18%) of the title compound as a pale yellow solid.

20

IR (KBr, cm⁻¹): 1706, 1615, 1469, 1152, 744.

¹H NMR (CDCl₃) δ 2.07 (s, 3 H), 2.66 (t, J = 6.5 Hz, 2 H), 4.57 (t, J = 6.5 Hz, 2 H), 6.36 (s, 2 H), 7.26-7.32 (m, 3 H), 7.35 (d, J = 1.0, 7.1 Hz, 1 H), 7.46 (dt, J = 0.9, 7.0 Hz, 1 H), 7.78-7.81 (m, 1 H), 7.85 (d, J = 8.3 Hz, 1 H), 8.03 (d, J = 8.3 Hz, 1 H).

25

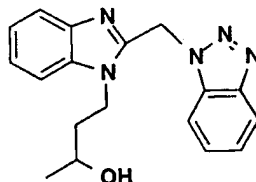
MS m/e 320 (MH⁺)

Anal. Calcd for C₁₈H₁₇N₅O • 0.5 H₂O: C, 65.84, H, 5.53; N, 21.33.

Found: C, 66.00; H, 5.28; N, 20.95.

30

5

Example 38**4-(2-Benzotriazol-1-ylmethyl)-benzimidazol-1-yl)-butan-2-ol**

10

1-(1H-Benzimidazol-2-ylmethyl)-1H-benzotriazole (0.30 g, 1.2 mmol), methyl vinyl ketone (126 mg, 1.8 mmol) and Triton B (40% in methanol, two drops) in pyridine (5 mL) were stirred at reflux overnight. The solvent was evaporated and the residue was dissolved in 5 mL of alcohol and sodium borohydride (91 mg, 2.4 mmol) was added. After stirring at room temperature for 2 hours, the reaction mixture was adjusted to pH 5 with concentrated HCl. The solvent was evaporated. The residue was diluted with water and extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography (EtOAc:hexane = 2:1 to straight EtOAc) to give a product which was triturated in hexane-ether to provide 81 mg (21%) of the product as a pale solid.

IR (KBr, cm⁻¹): 3369, 2959, 1458, 1426, 1103, 736.

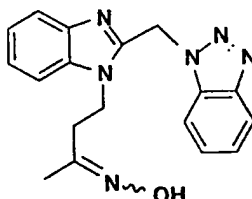
¹H NMR (CDCl₃) δ 1.14 (d, J = 6.2 Hz, 1 H), 1.40-1.59 (m, 2 H), 1.75 (d, J = 5.6 Hz, 1 H), 3.69-3.73 (m, 1 H), 4.07-4.55 (m, 2 H), 6.19 (d, J = 15.5 Hz, 1 H), 6.36 (d, J = 15.5 Hz, 1 H), 7.26-7.37 (m, 4 H), 7.44 (t, J = 8.0 Hz, 1 H), 7.77-7.84 (m, 2 H), 8.02 (d, J = 8.3 Hz, 1H).

MS m/e 322 (MH⁺).

Anal. Calcd for C₁₈H₁₉N₅O: C, 67.27, H, 5.96; N, 21.79

Found: C, 67.03; H, 6.15; N, 21.24

5

Example 394-(2-Benzotriazol-1-ylmethyl)-benzimidazol-1-yl)-butan-2-one, oxime

10

To a suspension of 4-(2-benzotriazol-1-ylmethyl)-benzimidazol-1-yl)-butan-2-one (24 mg, 0.075 mmol) in absolute ethanol (10 mL) was added triethylamine (8 mg, 0.075 mmol) followed by hydroxylamine hydrochloride (7.3 mg, 0.105 mmol). The mixture was refluxed overnight under nitrogen. The solvent was removed under reduced pressure. The resulting residue was diluted with saturated aqueous sodium bicarbonate and extracted with methylene chloride. The combined extracts were dried over magnesium sulfate, filtered and evaporated to give 25 mg (quantitative yield) of the title compound as a mixture of E and Z isomers.

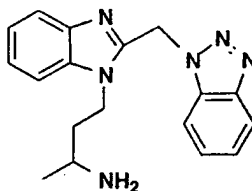
20

IR (KBr, cm^{-1}): 3064, 1473, 1422, 1083, 744.

^1H NMR (CDCl_3) δ 1.65 and 1.79 (s, 3 H), 2.50-2.60 (m 2 H), 4.54-4.59 (m, 2 H), 6.39 (s, 2 H), 7.15-7.45 (m, 3 H), 7.52-7.57 (m, 3 H), 7.80-7.87 (m, 1 H), 8.07-8.10 (m, 1 H).

25 MS m/e 335 (MH^+).

5

Example 403-(2-Benzotriazol-1-ylmethyl-benzimidazol-1-yl)-1-methyl-propylamine

10

To a solution of lithium aluminum hydride (8.4 mg, 0.318 mmol) in tetrahydrofuran (5 mL) at 0 °C, 4-(2-benzotriazol-1-ylmethyl)-benzimidazol-1-yl)-butan-2-one, oxime (24 mg, 0.071 mmol) in tetrahydrofuran (5 mL) was slowly added over 5 minutes. The reaction mixture was refluxed overnight. The reaction was quenched with 10 N NaOH (0.70 mL). The mixture was stirred over the weekend. The solution was decanted, and the solvent was stripped. Column chromatography (EtOAc:MeOH = 5:1 to 1:2) gave 8 mg (35% yield) of the product as a brown solid.

20

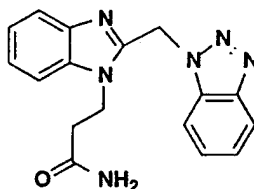
IR (KBr, cm^{-1}): 3435, 2933, 1575, 1423, 745.

^1H NMR (CDCl_3) δ 1.27 (d, $J = 7.5$ Hz, 3 H), 1.55-1.75 (m, 3 H), 3.30-3.37 (m, 1 H), 4.46-4.56 (m, 2 H), 6.23 (d, $J = 15.9$ Hz, 1 H), 6.30 (d, $J = 15.9$ Hz, 1 H), 7.24-7.54 (m, 5 H), 7.76-7.79 (m, 1 H), 7.82 (d, $J = 7.8$ Hz, 1 H), 7.96 (d, $J = 8.1$ Hz, 1 H).

25

MS m/e 321 (MH^+).

5

Example 413-(2-Benzotriazol-1-ylmethyl-1-H-benzimidazol-1-yl)-propionamide

10

1-(1H-Benzimidazol-2-ylmethyl)-1H-benzotriazole (300 mg, 1.20 mmol) and acrylamide (86 mg, 1.20 mmol) were dissolved in pyridine (5 mL). Triton B (40% by weight in methanol, 0.010 mL, 0.024 mmol) was added at room temperature. The temperature was slowly raised to reflux.

15 The reaction mixture was stirred at reflux overnight under nitrogen. The solvent was stripped under reduced pressure. The residue was taken up in aqueous saturated sodium bicarbonate solution and extracted with EtOAc (4x 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered and evaporated. The residue was purified by
20 chromatography (EtOAc/MeOH 12:1 to 4 : 1) to give 128 mg (33%) of the title compound as a white solid.

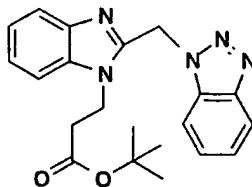
IR (KBr, cm^{-1}): 3778, 1675, 1467, 1455, 743.

^1H NMR ($\text{DMSO}-d_6$) δ 2.67 (t, $J = 6.4$ Hz, 2 H), 4.59 (t, $J = 6.4$ Hz, 2 H), 6.48 (s, 2 H), 7.02 (bs, 1 H), 7.16 (t, $J = 7.3$ Hz, 1H), 7.25 (t, $J = 7.3$ Hz, 1 H), 7.39-7.61 (m, 4H), 7.82 (d, $J = 8.3$ Hz, 1 H), 8.08 (d, $J = 8.3$ Hz, 1 H).

25

MS m/e 321 (MH^+).

5

Example 42t-Butyl 3-(2-benzotriazol-1-ylmethyl)-benzimidazol-1-yl)-propionate

10

1-(1H-Benzimidazol-2-ylmethyl)-1H-benzotriazole (0.30 g, 1.2 mmol), t-butyl acrylate (185 mg, 1.44 mmol) and Triton-B (40% in MeOH, two drops) in anhydrous pyridine (5 mL) were stirred at reflux over night. The solvent was evaporated, the residue was diluted with water, and
15 extracted with diethyl ether. The combined extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography (EtOAc: hexane = 1:2) to give 348 mg (77%) of the product as a solid.

20 IR (KBr, cm^{-1}): 1726, 1390, 1151, 736

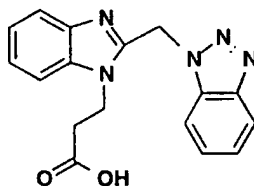
^1H NMR (CDCl_3) δ 1.36 (s, 9 H), 2.60 (t, $J = 6.5$ Hz, 2 H), 4.58 (t, $J = 6.5$ Hz, 2 H), 6.38 (s, 2 H), 7.27-7.35 (m, 4 H), 7.45 (t, $J = 7.0$ Hz, 1 H), 7.78-7.81 (m, 1 H), 7.88 (d, $J = 8.3$ Hz, 1 H), 8.02 (d, $J = 8.3$ Hz, 1 H).

MS m/e 378 (MH^+).

25 Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_2$: C, 66.83, H, 6.14; N, 18.55.

Found: C, 66.99; H, 6.17; N, 18.53.

5

Example 43**3-(2-Benzotriazol-1-ylmethyl)-benzimidazol-1-yl)-propionic acid**

10

t-Butyl 3-(2-benzotriazol-1-ylmethyl)-benzimidazol-1-yl)-propionate (100 mg, 0.27 mmol) was stirred in 50% trifluoroacetic acid in methylene chloride (3 mL) overnight. The solvent was evaporated, and the residue was diluted with saturated sodium bicarbonate solution, and 1 N HCl to pH 6. The solution was extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate and evaporated. The residue was triturated in a mixture of ethyl acetate and diethyl ether to give 71 mg (83%) of the product as a pale solid.

20 IR (KBr, cm^{-1}): 3420, 1705, 1441, 1269, 1212, 744.

^1H NMR (DMSO-d_6) δ 2.77 (t, $J = 6.9$ Hz, 2 H), 4.60 (t, $J = 6.9$ Hz, 2 H), 6.46 (s, 2 H), 7.15-7.28 (m, 2 H), 7.43 (t, $J = 7.0$ Hz, 1 H), 7.52-7.57 (m, 2 H), 7.63 (d, $J = 8.0$ Hz, 1 H), 7.83 (d, $J = 8.3$ Hz, 1 H), 8.09 (d, $J = 8.3$ Hz, 1 H).

MS m/e 322 (MH^+).

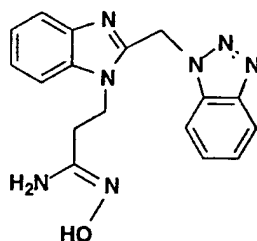
25 Anal. Calcd for $\text{C}_{17}\text{H}_{15}\text{N}_5\text{O}_2$: C, 63.54; H, 4.70; N, 21.79.

Found: C, 63.35; H, 4.88; N, 21.84.

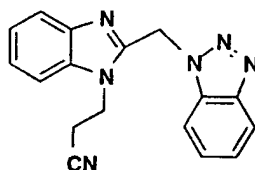
5

Example 44N-[3-(2-Benzotriazol-1-ylmethyl-benzimidazol-1-yl)-1-imino-propyl)-hydroxyamine

10

3-(2-Benzotriazol-1-ylmethyl-1-H-benzimidazol-1-yl)-propionitrile

15



To 1-(1H-benzimidazol-2-ylmethyl)-1H-benzotriazole (100 mg, 0.40 mmol) suspended in 5 mL of acetonitrile under nitrogen atmosphere was added acrylonitrile (0.032 mL, 0.48 mmol), followed by 1,3,4,6,7,8-hexahydro-1-methyl-2H-pyrimido[1,2-a] pyrimidine (MTBD, 0.003 mL, 0.020 mmol). The reaction mixture was heated to 80°C for 6 hours. The solvent was stripped. The residue was taken up in ether and washed with water. Column chromatography (EtOAc/hexane = 10:1) of the residue gave 45 mg (37%) of the product as a pale yellow solid.

25

IR (KBr, cm⁻¹): 3057, 2921, 2255, 1616, 1461, 1329, 739

¹H NMR (CDCl₃) δ 2.65 (t, J = 6.6 Hz, 2 H), 4.70 (t, J = 6.6 Hz, 2 H), 6.25 (s, 2 H), 7.30-7.40 (m, 4 H), 7.47-7.52 (m, 1 H), 7.81-7.87 (m, 2 H), 8.04 (d, J = 8.4 Hz, 1 H)

5 MS m/e 303 (MH⁺).

Anal. Calcd for C₁₇H₁₄N₆ • 0.25 H₂O: C, 66.54; H, 4.76; N, 27.39

Found: C, 66.53; H, 4.60; N, 27.19

3-(2-Benzotriazol-1-ylmethyl-1-H-benzimidazol-1-yl)-propionitrile
10 (100 mg, 0.33 mmol), hydroxylamine hydrochloride (83 mg, 1.19 mmol)
and potassium carbonate (87 mg, 0.63 mmol) were dissolved in a mixture
of ethanol and water (2:1, 7.5 mL). The solution was stirred at room
temperature for 10 minutes and then at reflux overnight. The solvent
was evaporated, and the residue diluted with water and extracted with
15 methylene chloride (3 x 50 mL). The combined organic fractions were
dried over magnesium sulfate, and evaporated. Column chromatography
(EtOAc to EtOAc:MeOH=10:1, gradient) gave 71 mg (64% yield) the title
compound as a pale yellow solid.

20 IR (KBr, cm⁻¹): 3110, 1670, 1473, 1422, 747.

¹H NMR (CDCl₃) δ 2.18 (t, J = 7.5 Hz, 2 H), 4.60 (t, J = 7.5 Hz, 2 H), 4.79 (bs, 2
H), 6.23 (s, 2 H), 7.25-7.47 (m, 5 H), 7.80-7.82 (m, 1 H), 7.84 (d, J = 7.5 Hz, 1 H),
8.02 (d, J = 8.4 Hz, 1 H).

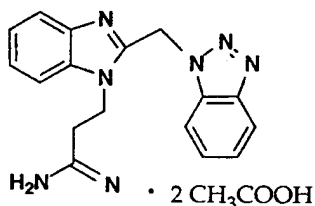
MS m/e 336 (MH⁺).

25

5

Example 45**3-(2-Benzotriazol-1-ylmethyl-benzimidazol-1-yl)-1-imino-propyl-amine****Diacetate**

10



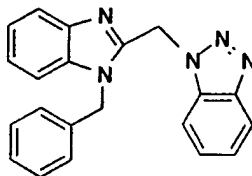
N-[3-(2-Benzotriazol-1-ylmethyl-benzimidazol-1-yl)-1-imino-propyl]-hydroxyamine (57 mg, 0.17 mmol) was dissolved in acetic acid (1 mL). Acetic anhydride was added and the solution was stirred at room temperature for 5-10 minutes. The solution was then added to 10% Pd/C (15 mg) in a Parr reaction vessel. The mixture was agitated under H₂ (at 55 psi) for 4 hours. The catalyst was removed by filtration. Evaporation of the filtrate gave a yellow gum which was azeotroped with hexane several times. Trituration with diethyl ether gave 64 mg (64% yield) of the title compound as a tan solid.

IR (KBr, cm⁻¹): 3027, 1685, 1513, 1281, 746.

¹H NMR (DMSO-d₆) δ 1.81 (s, 6 H), 2.94 (t, J = 7.4 Hz, 2 H), 4.75 (t, J = 7.4 Hz, 2 H), 6.46 (s, 2 H), 7.20 (t, J = 7.3 Hz, 1 H), 7.30 (t, J = 7.2 Hz, 1 H), 7.45 (t, J = 8.1 Hz, 1 H), 7.51-7.61 (m, 2 H), 7.74 (d, J = 8.0 Hz, 1 H), 7.88 (d, J = 8.3 Hz, 1 H), 8.11 (d, J = 8.4 Hz, 1 H).

MS m/e 320 (MH⁺).

5

Example 461-[(1-Phenylmethyl-1H-benzimidazol)-2-ylmethyl]-1H-benzotriazole

10

The general coupling procedure was applied using benzyl bromide and sodium hydride in tetrahydrofuran to give the title compound in 95% yield:

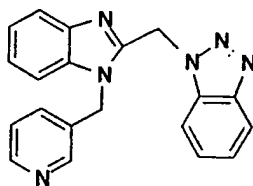
15 IR (KBr, cm^{-1}): 1494, 1436, 1323, 1227, 753, 729.

^1H NMR (CDCl_3) δ 5.48 (s, 2 H), 6.14 (s, 2 H), 6.84 (dd, $d = 8.0$ Hz, 1 H), 6.83-7.45 (m, 9 H), 7.79 (d, $J = 8.2$ Hz, 1 H), 7.86 (d, $J = 7.1$ Hz, 1 H), 7.94 (d, $J = 8.1$ Hz, 1 H).

MS m/e 340 (MH^+).

20 Anal. Calcd for $\text{C}_{21}\text{H}_{17}\text{N}_5 \cdot 0.25\text{H}_2\text{O}$: C, 73.34; H, 5.13; N, 20.36
Found: C, 73.62; H, 5.22; N, 20.28

5

Example 471-[1-(Pyridin-3-yl-methyl)-1H-benzimidazol-2-ylmethyl]-1H-benzotriazole

10

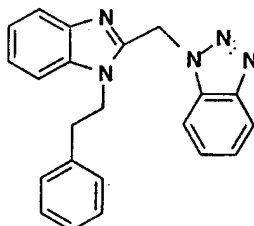
The general coupling procedure was applied using 3-picolyl chloride hydrochloride and sodium hydride in tetrahydrofuran to give the title compound in 31% yield:

15 IR(KBr, cm^{-1}): 3423, 1578, 1452, 1425, 1335, 1240, 1089, 749.

^1H NMR (CDCl_3) δ 5.53 (s, 2 H), 6.17(s, 2 H), 6.97-6.99 (m 1 H), 7.44 (t, $J = 7.0$ Hz, 1 H), 7.17 -7.37 (m, 7 H), 7.76 (d, $J = 8.3$ Hz, 1 H), 7.88 (d, $J = 8.0$ Hz, 1 H), 7.93 (d, $J = 7.5$ Hz, 1 H).

MS m/e 341 (MH^+).

5

Example 481-[1-(2-Phenethyl)-1-H-benzimidazol-2-ylmethyl]-1H-benzotriazole

10

1-(1H-Benzimidazol-2-ylmethyl)-1H-benzotriazole (374 mg, 1.5 mmol), phenethyl alcohol (0.12 mL, 1.0 mmol), and tributylphosphine (0.37 mL, 1.5 mmol) were mixed in 10 mL of anhydrous benzene under nitrogen. The mixture was cooled in an ice bath, and 1,1'-(azodicarbonyl)-
15 dipiperidine (378 mg, 1.5 mmol) was added. After stirring for 15 minutes at 0°C, the reaction was allowed to warm to room temperature and stirred overnight. The solvent was evaporated and column chromatography of the residue (EtOAc/hexane = 1:1 to EtOAc/hexane=3:1, gradient) gave the title compound as a pale yellow solid (63 mg, 18% yield).

20

IR (KBr, cm^{-1}): 1615, 1495, 1471, 1454, 1075, 744

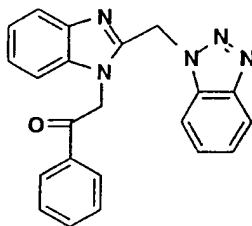
^1H NMR (CDCl_3) δ 2.76 (t, $J = 7.1$ Hz, 2 H), 4.42 (t, $J = 7.1$ Hz, 2 H), 5.54 (s, 2 H), 6.95 (bd, $J = 7.8$ Hz, 2 H), 7.19-7.37 (m, 8 H), 7.68 (d, $J = 8.4$ Hz, 1 H), 7.75-7.78 (m, 1 H), 7.95 (d, $J = 7.9$ Hz, 1 H).

25 MS m/e 354 (MH^+).

Anal. Calcd for $\text{C}_{22}\text{H}_{19}\text{N}_5 \cdot 0.25 \text{H}_2\text{O}$: C, 73.83; H, 5.49; N, 19.57

Found: C, 73.72; H, 5.48; N, 19.24

5

Example 492-[(2-Benzotriazol-1-ylmethyl)-benzimidazol-1-yl]-1-phenyl-ethanone

10

The general coupling procedure was applied using 2-bromoacetophenone and sodium hydride in N, N-dimethylformamide to give the title compound in 27% yield:

15

IR (KBr, cm^{-1}): 1697, 1466, 1449, 747

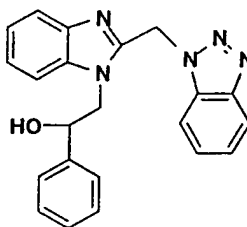
^1H NMR (DMSO- d_6) δ 2.71 (s, CH_3 , DMF), 2.87 (s, CH_3 , DMF), 6.22 (s, 2 H), 6.29 (s, 2H), 7.14-7.22 (m, 2 H), 7.34-7.39 (m, 1 H), 7.48-7.53 (m, 4 H), 7.56-7.65 (m, 2 H), 7.99 (s, HCO , DMF), 8.02-8.05 (m, 4 H).

20 MS m/e 368 (MH^+).

Anal Calc for $\text{C}_{22}\text{H}_{17}\text{N}_5\text{O} \cdot 1.7 \text{H}_2\text{O} \cdot 2.1 \text{DMF}$: C, 61.63; H, 6.41; N, 18.03

Found: C, 61.48; H, 6.13; N, 17.87

5

Example 502-[(2-Benzotriazol-1-ylmethyl)-benzimidazol-1-yl]-1-phenyl-ethanol

10

To a solution of 2-[(2-benzotriazol-1-ylmethyl)-benzimidazol-1-yl]-1-phenyl-ethanone (120 mg, 0.33 mmol) in methanol (5 mL) was added sodium borohydride (124 mg, 3.26 mmol) at 0°C. The reaction mixture was stirred at 0°C for 2 hours and then at room temperature for additional
15 2 hours. Methanol was removed and the residue was diluted with water and extracted with methylene chloride. The combined organic extracts were dried over sodium sulfate and evaporated to give 71 mg (59% yield) of the title compound as a white solid.

20 IR(KBr, cm⁻¹): 3209, 1453, 1430, 744, 699.

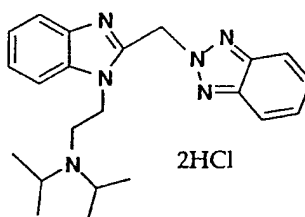
¹H NMR (DMSO-d₆) δ 4.41-4.53 (m, 2 H), 4.87-4.91 (m, 1 H), 5.91 (d, J = 4.2 Hz, 1 H), 6.25 (d, J = 16.5 Hz, 1 H), 6.37 (d, J = 16.5 Hz, 1 H), 7.11-7.28 (m, 2 H), 7.31-7.42 (m, 4 H), 7.47-7.60 (m, 5 H) 7.75 (d, J = 8.3 Hz, 1 H), 8.06 (d, J = 8.3 Hz, 1 H)

25 MS m/e 370 (MH⁺)

Anal. Calc for C₂₂H₁₉N₅O • 0.25 EtOAc • 0.1 H₂O: C, 66.30; H, 5.76; N, 16.81

Found: C, 66.19; H, 5.38; N, 17.06

5

Example 57[2-(2-Benzotriazol-2-ylmethyl)-benzimidazol-1-yl]-ethyl]-diisopropyl-amine Dihydrochloride

10

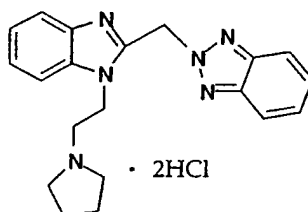
The general coupling procedure was applied using 2-(1H-benzimidazol-2-ylmethyl)-2H-benzotriazole, 2-diisopropylaminoethyl chloride hydrochloride and sodium hydride in N,N-dimethylformamide to give the title compound in 15% yield:

IR (KBr, cm^{-1}) 3400, 2973, 2654, 1461, 1328, 1140, 750.
 ^1H NMR (CD_3OD) δ 1.46 (d, $J = 6.4$ Hz, 6 H), 1.52 (d, $J = 6.4$ Hz, 6 H), 3.66-3.69 (m, 2 H), 3.91-4.00 (m, 2 H), 5.26-5.32 (m, 2 H), 6.67 (s, 2 H), 7.47-7.50 (m, 2 H), 7.64-7.70 (m, 2 H), 7.88-7.91 (m, 2 H), 8.05 (d, $J = 8.4$ Hz, 1 H).
MS m/e 377 (MH^+).

Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{N}_6 \cdot 2\text{HCl} \cdot 1.25 \text{H}_2\text{O}$: C, 55.99; H, 6.94; N, 17.81

Found: C, 56.01; H, 6.74; N, 17.46

5

Example 582-(2-Pyrrolidin-1-yl-ethyl)-1H-benzimidazol-2-ylmethyl)-2H-benzotriazole
Dihydrochloride

10

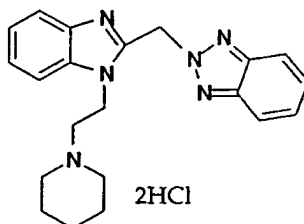
The general coupling procedure was applied using 2-(1H-benzimidazol-2-ylmethyl)-2H-benzotriazole, 1-(2-chloroethyl)-pyrrolidine hydrochloride and sodium hydride in toluene to give the title compound
15 in 38% yield:

IR(KBr, cm^{-1}): 3390, 2962, 2474, 1529, 1462, 1267.

^1H NMR (CD_3OD) δ 2.05-2.15 (m, 4 H), 3.56-3.85(m, 6 H), 5.21-5.26 (m, 2 H),
6.75 (s, 2), 7.48-7.52 (m, 2 H), 7.64-7.75 (m, 2 H), 7.84 (d, $J = 7.7$ Hz, 1 H), 7.90-
20 7.94 (m, 2 H) 8.105 (d, $J = 8.1$ Hz, 1 H),

MS m/e 347 (MH^+).

5

Example 592-(2-Piperidin-1-yl-ethyl)-1H-benzimidazol-2-ylmethyl)-2H-benzotriazole
Dihydrochloride

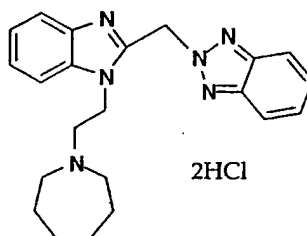
The general coupling procedure was applied using 2-(1H-benzimidazol-2-ylmethyl)-2H-benzotriazole, 1-(2-chloroethyl)-piperidine hydrochloride and sodium hydride in toluene to give the title compound
15 in 65% yield:

IR(KBr, cm^{-1}): 3435, 2916, 2721, 1728, 1615, 1452, 1417, 1276, 758.

^1H NMR (CD_3OD) δ 1.90-2.10 (m, 6 H), 3.10-3.20 (m, 2 H), 3.56-3.76 (m, 4 H),
5.21-5.34 (m, 2 H), 6.76 (s, 1 H), 7.48-7.53 (m, 2 H), 7.60-7.75 (m, 2 H), 7.83 (d,
20 $J = 7.7$ Hz, 1H), 7.90-7.94 (m, 2 H), 8.16 (d, $J = 8.1$ Hz, 1 H).

MS m/e 361 (MH^+).

5

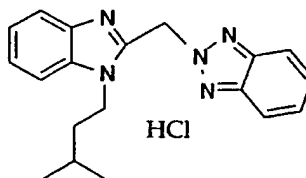
Example 60**2-(2-Azepin-1-yl-ethyl)-1H-benzimidazol-2-ylmethyl)-2H-benzotriazole**
Dihydrochloride

10

The general coupling procedure was applied using 2-(1H-benzimidazol-2-ylmethyl)-2H-benzotriazole and 2-(hexamethyleneimino)ethyl chloride hydrochloride and sodium hydride
15 in tetrahydrofuran to give the title compound in 39% yield:

IR(KBr, cm^{-1}): 3430, 2926, 1617, 1526, 1456, 744.

^1H NMR (CD_3OD) δ 1.75-1.80 (m, 4 H), 1.85-2.10 (m, 4 H), 3.32-3.42 (m, 2 H),
3.67-3.72 (m, 4 H), 5.22-5.27 (m, 2 H), 6.71 (s, 2 H), 7.49-7.52 (m, 2 H), 7.63-
20 7.72 (m, 2 H), 7.83 (d, $J = 7.6$ Hz, 7.90-7.95 (m, 2 H). 8.07 (d, $J = 7.9$ Hz, 1 H).
MS m/e 375 (MH^+).

Example 61**2-[1-(3-methylbutyl)-1H-benzimidazol-2-ylmethyl]-2H-benzotriazole**
Dihydrochloride

5

The general coupling procedure was applied using 2-(1H-benzimidazol-2-ylmethyl)-2H-benzotriazole, 1-bromo-3-methylbutane and sodium hydride in N,N-dimethylformamide to give the title compound in 30% yield:

10

IR (KBr, cm^{-1}): 2959.8, 1623.0, 1538, 1326.3, 754.

^1H NMR (DMSO-d_6) δ 0.91 (d, $J = 6.6$ Hz, 6 H), 1.37-1.45 (m, 2 H); 1.65-1.75 (m, 1H), 4.62-4.68 (m, 2 H), 6.67 (s, 2H), 7.48-7.56 (m, 2H), 7.69-7.74 (m, 2 H), 7.86-7.94 (m, 4H).

15 MS m/e 320 (MH^+)

Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{N}_5 \cdot \text{HCl} \cdot 3/4 \text{H}_2\text{O}$: C, 61.78; H, 6.65; N, 18.96; Cl, 9.60.

Found: C, 61.87; H, 6.50; N, 18.98; Cl, 9.65.

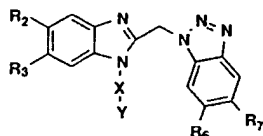
5 BIOLOGICAL ACTIVITY

The antiviral activity of these compounds against respiratory syncytial virus was determined in HEp-2 (ATCC CCL 23) cells that were seeded in 96 well microtiter plates at 1.5×10^4 cells/100 μ L/well in DMEM (Dulbecco's Modified Eagle's Medium) supplemented with penicillin, streptomycin, glutamine, and 10% fetal bovine serum. The cells were incubated overnight at 37 °C, the culture medium was removed, and cells were infected (100 μ L volume in medium containing 2% fetal bovine serum) with respiratory syncytial virus Long strain at 5000 plaque forming units/mL. The compounds, 100 μ L at appropriate dilution, were added to the cells 1 hour post infection. After incubation for 4 days at 37 °C, the plates were stained with MTT solution (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) and incubated for 4 hours at 37 °C. The media was aspirated from the cells and 100 μ L/well of acidified isopropanol (per liter: 900 ml isopropanol, 100 ml Triton X100, and 4 ml conc. HCl) was added. Plates were incubated for 15 minutes at room temperature with shaking, and an optical density (OD 540) reading at 540 nanometer (nm) was obtained. The optical density reading is proportional to the number of viable cells. The increase in the number of viable cells reflects the protective, antiviral activity of the compound. Assays comparing MTT staining in uninfected cells containing compound with uninfected cells in the absence of compound provide a measure of cellular toxicity. The control compound in this assay is Ribavirin which exhibits 100% cell protection at 2.5 μ g/mL (corresponding to 10.2 μ M).

The antiviral activity of compounds is presented as a percentage of cell protection at a concentration of 4 μ g/mL of the compound. The higher percentage of cell protection, the more potent is the compound.

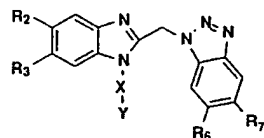
- 5 The CC_{50} values, expressed in micromolars (μM), represent the concentration of the compound that results in a normalized OD540 reading half that of uninfected cells not treated with compound. The lower the concentration, the more cytotoxic is the compound. The CC_{50} for Ribavirin in this assay is $9.5 \mu g/mL$ (corresponding to $40 \mu M$). The data
- 10 are shown in Table 1 and 2.

Table 1.



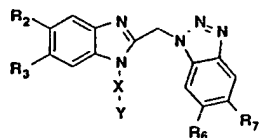
Example No.	R ₂	R ₃	R ₆ and R ₇	X-Y	% Cell protection at 4 µg/mL	CC ₅₀ (µM)
1	H	H	H		100	> 100
2	H	H	H		100	197
3	H	H	H		100	215
4	H	H	H		100	166
5	CH ₃ CO	H	H		100	102
6	CF ₃	H	H		100	84
7	CF ₃	H	H		95	28
8	NO ₂	H	H		91	127
9	H	H	H		100	236
10	H	H	H		55	42
11	Me	Me	H		100	92
12	Cl	Cl	H		97	18
13	H	H	Me		90	118
14	H	H	H		90	80
15	H	H	H		92	75
16	H	H	H		73	67
17	H	H	H		53	24
18	H	H	H		54	105

Table 1 (cont.)



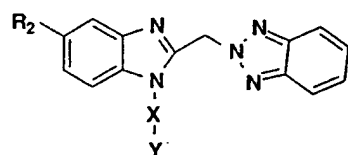
Example No.	R ₂	R ₃	R ₆ and R ₇	X-Y	% Cell protection at 4 µg/mL	CC ₅₀ (µM)
19	H	H	H		95	12
20	H	H	H		87	40
21	H	H	H		98	69
22	H	H	H		75	15
23	H	H	H		98	59
24	H	H	H		100	165
25	H	H	H		100	56
26	H	H	H		100	200
27	H	H	H		44	117
28	H	H	H		61	29
29	H	H	H		98	185
30	H	H	H		90	108
31	H	H	H		48	21
32	H	H	H		60	71
33	H	H	H		82	75
34	H	H	H		81	86

Table 1 (cont.)



Example No.	R ₂	R ₃	R ₆ and R ₇	X-Y	% Cell protection at 4 µg/mL	CC ₅₀ (µM)
35	H	H	H		58	230
36	H	H	H		100	74
37	H	H	H		100	59
38	H	H	H		100	>309
39	H	H	H		100	>33
40	H	H	H		96	8.5
41	H	H	H		75	4.3
42	H	H	H		100	168
43	H	H	H		82	>309
44	H	H	H		91	16
45	H	H	H		74	6.3
46	H	H	H		53	97
47	H	H	H		40	250
48	H	H	H		95	2.6
49	H	H	H		76	18
50	H	H	H		94	36

Table 2.

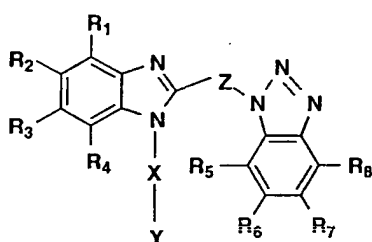


<u>Example No.</u>	<u>R₂</u>	<u>X-Y</u>	% Cell protection at 4 µg/mL	CC ₅₀ (µM)
51	H	NMe ₂	100	212
52	H	NMe ₂	89	182
53	H	NEt ₂	78	83
54	Cl	NEt ₂	100	82
55	CH ₃ CO	NEt ₂	56	185
56	CF ₃	NEt ₂	83	99
57	H	N(i-Pr) ₂	100	42
58	H	N-propylpyrrolidine	92	140
59	H	N-propylpiperidine	87	65
60	H	N-propylpiperazine	77	23
61	H	N-propyl-2-methylbutylamine	78	27

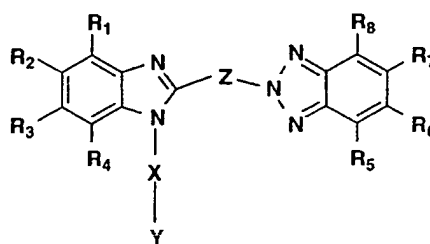
CLAIMS

What is claimed is:

1. A compound having the Formula II or Formula III, and
10 pharmaceutically acceptable salts thereof,



Formula II



Formula III

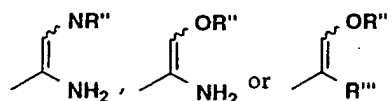
wherein:

- 15 $R_1, R_2, R_3, R_4, R_5, R_6, R_7$ and R_8 are independently H, alkyl, alkyl substituted with 1 to 6 halogen atoms, NO_2 , CN, halogen, COR' , $COOR'$, and $CONHR'$, R' is H or alkyl, and said alkyl contains 1 to 6 carbon atoms;
- 20 X is straight, branched or cyclic alkyl, alkenyl, and alkynyl groups, wherein said groups have 2 to 12 carbon atoms;

Y is selected from:

- 25 (a) R_9 , $-NR_9R_{10}$, $-^*NR_9R_{10}R_{11}$, $-NHCOR_9$, $=N-O-R_9$;
 $-CONHR_9$, $-COOR_9$, $-CO-R_9$, $-OR_9$,
 wherein R_9 , R_{10} and R_{11} are independently H, straight,
 branched or cyclic alkyl containing 1 to 7 carbon atoms; or
 R_9 taken together with R_{10} forms a cyclic alkyl group
 30 having 3 to 7 carbon atoms;

- 5 (b) $-N_3$, $-CN$, halogen, $-NO_2$, $-NR''SO_2R'''$,
 $-SR''$, $-SOR''$, $-SO_2R''$, $-SO_2NR''$,

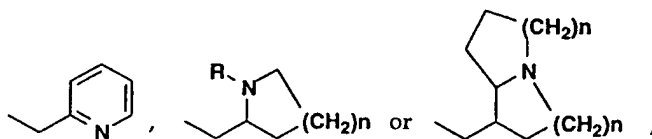


- 10 wherein said R'' and R''' are independently hydrogen,
 C_1 - C_6 alkyl, phenyl, or phenyl substituted with from 1 to 6
halogen atoms or C_1 - C_6 alkyl groups;

- (c) phenyl or heterocycle, selected from dioxolane, pyridine,
pyrrole, thiophene, pyrrolidine or piperidine, and
15 wherein said phenyl is optionally substituted with from
1 to 6 halogen atoms or C_1 - C_6 alkyl groups;

or X and Y taken together is selected from $-CH_2Ph$, $-CH_2COPh$,
 $-CH_2CHOHPh$,

20



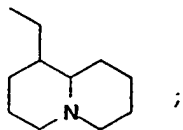
wherein n is 1 or 2, R is C_1 - C_4 alkyl and Ph is phenyl;

- 25 Z is $-(CR_{12}R_{13})_n-$, wherein n is 1-4, and R_{12} and R_{13} are independently H,
straight, branched or cyclic C_1 - C_6 alkyl;

provided when R_2 is H, Cl, CF_3 , CH_3CO or NO_2 ; R_1 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8
are not at the same time H; Z is not $(CH_2)_n$, where n is 1-3; X is not $(CH_2)_z$,
where z is 2 or 3; Y is not $N(CH_3)_2$ or $N(C_2H_5)_2$ or X and Y taken together is

30

not



5

further provided when X and Y taken together is $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, then Z is not CH_2 and $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5, \text{R}_6, \text{R}_7$ and R_8 are not each H at the same time.

10 2. A compound of claim 1 wherein:

$\text{R}_1, \text{R}_3, \text{R}_4, \text{R}_5, \text{R}_6, \text{R}_7$ and R_8 are each H; R_2 is H, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_3$ alkyl substituted with 1 to 6 halogen atoms, NO_2 , CN, halogen, COR' , COOR' , or CONHR' , wherein R' is H or $\text{C}_1\text{-C}_3$ alkyl;

15

X is $-(\text{CH}_2)_2-$ or $-(\text{CH}_2)_3-$;

Y is selected from

20

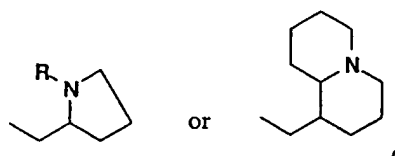
(a) H, straight, branched or cyclic $\text{C}_1\text{-C}_7$ alkyl;
 $-\text{NR}_9\text{R}_{10}$, $-\text{NR}_9\text{R}_{10}\text{R}_{11}$, $-\text{NHCOR}_9$, $-\text{CO-R}_9$, $-\text{OR}_9$, wherein R_9 and R_{10} are independently H, straight or branched $\text{C}_1\text{-C}_3$ alkyl; or R_9 taken together with R_{10} forms a cyclic alkyl group having 5 to 7 carbon atoms;

25

(b) $-\text{NHSO}_2\text{R}''$, $-\text{SR}''$, $-\text{SOR}''$, $-\text{SO}_2\text{R}''$, wherein said R'' is $\text{C}_1\text{-C}_3$ alkyl;

or X and Y taken together is selected from $-\text{CH}_2\text{COPh}$, $-\text{CH}_2\text{CHOHPh}$,

30



wherein R is $\text{C}_1\text{-C}_3$ alkyl; and

5 Z is CH₂.

3. A compound of claim 1 wherein:

R₁, R₃, R₄, R₅, R₆, R₇ and R₈ are each H; R₂ is H or halogen;

10

X is -(CH₂)₂- or -(CH₂)₃;

Y is selected from

15 (a) H, straight, branched or cyclic C₁-C₇ alkyl;
-NR₉R₁₀, -NR₉R₁₀R₁₁, -CO-R₉, or -OR₉, wherein R₉ and
R₁₀ are independently H, straight, branched C₁-C₃ alkyl; or
R₉ taken together with R₁₀ forms a cyclic alkyl group
having 5 to 7 carbon atoms;

20

(b) -SR'', -SOR'' or -SO₂R'', wherein said R'' is CH₃;

or X and Y taken together is -CH₂COPh or -CH₂CHOHPh; and

25 Z is CH₂.

4. A method for treating mammals infected with RSV, and in need thereof, which comprises administering to said mammal a therapeutically effective amount of a compound having the Formula II or Formula III,
30 and pharmaceutically acceptable salts thereof, as claimed in any one of claims 1-3, but not subject to the proviso thereto.

5. A pharmaceutical composition which comprises a therapeutically effective amount of an anti-RSV compound having Formula II or
35 Formula III, and pharmaceutically acceptable salts thereof, as claimed in any one of claims 1-3, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12398

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, MEDLINE, BIOSIS

search terms: respiratory(L)syncytial(L)virus, RSV, benzotriazol?, benzimidazol?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,324,794 A (TIDWELL et al) 13 April 1982, entire document.	1-5
A	US 5,066,656 A (GRECO et al) 19 November 1991, col. 1, lines 26-68; col. 2, lines 1-68; col. 3, lines 1-68.	1-3
A	DUBOVI et al. Inhibition of Respiratory Syncytial Virus by Bis(5-amidino-2- benzimidazolyl)methane. Virology. June 1980, Vol. 103, No. 2, pages 502-504.	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

02 SEPTEMBER 1999

Date of mailing of the international search report

07 OCT 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JANE C. OSWECKI

Telephone No. (703)308-1235

JOYCE BRIDGERS
PARALEGAL SPECIALIST
CHEMICAL MATRICES

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/12398

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 31/335, 31/38, 31/40, 31/41, 31/415, 31/44, 31/445, 31/55; C07D 207/09, 207/44, 211/26, 211/28, 213/04, 223/04, 213/12, 235/04, 235/06, 235/12, 235/14, 249/16, 249/18, 317/08, 317/28, 333/02, 333/04, 333/26, 333/36, 403/06, 405/06, 409/06, 487/02, 487/04

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/212, 322, 338, 339, 359, 397, 399, 413, 414, 422, 427, 444, 467; 540/484, 524, 531, 603; 546/199, 268.4, 273.4; 548/257, 260, 305.1, 306.1, 524, 453, 455; 549/59, 430, 448, 451

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/212, 322, 338, 339, 359, 397, 399, 413, 414, 422, 427, 444, 467; 540/484, 524, 531, 603; 546/199, 268.4, 273.4; 548/257, 260, 305.1, 306.1, 524, 453, 455; 549/59, 430, 448, 451